"ROLE OF HYPERFRACTIONATED RADIOTHERAPY WITH WEEKLY DOCETAXEL IN LOCALLY ADVANCED UNRESECTABLE HEAD AND NECK CANCER"

Dissertation submitted in partial fulfillment of

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CERTIFICATE

This is to certify that **DR.S.JEYASANKAR** has been a postgraduate student during the period of May 2013 to March 2016 in the Department of Radiotherapy, Madras Medical College, Rajiv Gandhi Govt. General Hospital, Chennai.

This Dissertation titled **"Role of Hyperfractionated Radiotherapy with Weekly Docetaxel in Locally Advanced Unresectable Head and Neck Cancer"** is a work done by him during the study period and is being submitted to the Tamil Nadu Dr.M.G.R Medical University in partial fulfillment of M.D Branch IX Radiotherapy Examination.

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DECLARATION

I hereby declare that the dissertation entitled **"Role of Hyperfractionated Radiotherapy with Weekly Docetaxel in Locally Advanced Unresectable Head and Neck Cancer"** submitted for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch-IX, RADIOTHERAPY is my unique work. The dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai
Date:

Signature of the Scholar

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CONTENTS

ABSTRACT

TITLE: "ROLE OF HYPERFRACTIONATED RADIOTHERAPY WITH WEEKLY DOCETAXEL IN LOCALLY ADVANCED UNRESECTABLE HEAD AND NECK CANCER"

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Aims And Objectives:

To assess the immediate loco regional response rates of locally advanced unresectable squamous cell carcinomas of the head and neck cancer treated with hyperfractionated radiotherapy and concurrent weekly Docetaxel.

To assess the acute toxicities of the treatment.

Materials And Methods:

Eligible 30 patients were taken up for concurrent chemotheraphy with hyperfractionated radiotherapy 120 centigray twice daily fractions with a gap of 6 hours, 5 days in a week along with inj.docetoxel 20 mg/m^2 weekly. Patients were assessed clinically during treatment for toxicity and response 6 weeks after completion of treatment .

Results:

Female sex showed higher complete responses than male. Stage-III cancers shows higher complete responses than stage IV A. Moderately and poorly differentiated cancers showed a considerable complete response. Lower the T stage higher is the complete response. Lower the N stage higher is the complete response and lower the TNM stage group higher is the complete response. Hypopharyngeal and oropharyngeal tumors produced greater complete response. Complete response rate in primary T3 and T4A tumors are 90% and 70% respectively. Complete response rates attained by N0, N1, N2A, and N2C nodes are 100%, 90%, 50% and 63% respectively. Primary and secondary complete response was achieved by 76% high complete responses were achieved by T3N0 (100%), T3 N1 (100%), then by T3N2A(50%),T3 N2C (66.66%),T4A N1 (70%) and last by T4A N2C (60%). 63.33% had grade 3 mucositis. 73.33% had grade 2 and 3.33% had grade 3 skin toxicities. 10% had grade 3 laryngitis. No grade 3, 4 hematological toxicities and in anemia. No Grade 3, 4 hematological toxicities in leucopenia or thrombocytopenia were observed. There was no grade III or IV vomiting.

Conclussion

Docetaxel is one of the effective agent in head and neck cancers with manageable toxicities. This study shows that concurrent chemo radiotherapy using hyperfractionated radiotherapy combined with low dose weekly docetaxel produces complete response rate 76%.

Keywords. Hyperfractionated RT, concurrent chemotherapy, docetaxel, head and neck cancer

INTRODUCTION

GLOBAL BURDEN OF HEAD AND NECK CANCER

The number of newly diagnosed cancers worldwide in 2008 was approximately 12.7 million, with 5.6 million cases from the economically more developed countries and 7.1 million from the less developed countries **[9].** Worldwide 560,000 cases of head and neck cancer are diagnosed every year, and 300,000 patients died because of it. [10].

In 2009, 48010 new head and neck cancer cases have been detected in United States and this represents 3.2% of the total new cancer load [6]. Two thirds of the new cancer cases diagnosed in the world are from developing countries like India. Southeast Asia will face sudden increase in number of cancer deaths more than 50%. High rate of occurrence of oral cavity cancers is reported from Australia, India, South Africa and Western Europe. [11] Cancer incidence rate is maximum in India among the SAARC countries [3].

INDIAN BURDEN OF HEAD AND NECK CANCER

Head and neck cancers are the 2nd most common cancers in men and fourth most common cancer in women in India [3]. Head and neck cancers are the most common cause of death in the 25 to

60 years age group following cardiovascular disease, respiratory disease and tuberculosis [3].

At present the total population of India is 1.2 billion. At any given point of time there are 240 thousand cancer patients according to WHO report [3,28]. Head and neck cancers contribute to the total incidence of cancer around 33% in India whereas it is only 10% in western countries [5] .*The estimates of head and neck cancer in men for the year 2015,it is 1lakh 53 thousand in men and 64 thousand in women [7].*

TAMILNADU

Most common cancer in men is ***head and neck cancer (19.23%)*** followed by stomach cancer (13.98%) and then by lung cancer (12.46%).In women, breast cancer is the most common (20.87%) followed by cervical cancer (11.46%) then by stomach cancer (8.11%) and ***head and neck cancer (7.53%).*** Tobacco use is the major cause for head and neck cancer in tamilnadu[8]. The incidence of oral cavity cancers shows a rising trend.

Head and neck is the most essential structure for physiological functions like respiration, nourishment, verbal communication and appearance, which are only one of its kind.

Any kind of surgical procedure, reconstruction, radiation and chemotherapy induced toxicities has got a lot of difficulties over the normal physiological functions; causes disfigurement and decreases the quality of life.

ETIOLOGY

It is estimated that most of cancer deaths are due to tobacco, alcohol consumption, harmful dietary habits, and infection [4].Among the causes, tobacco use in any form is the world's most preventable cause for head and neck cancer. There are one billion smokers and millions of smokeless tobacco users in the world [1, 2].

EPIDEMIOLOGY OF TOBACCO

In India, 274.9 million tobacco users there; 163.7 million people using smokeless form of tobacco; 68.9 million adults use smoking form of tobacco only and 42.3 million people utilize both smoking and smokeless forms of tobacco.14.1% of children age between 13 and 15 years use tobacco. In general tobacco usage among men is around 48% and in women it is 20%.

SMOKING TOBACCO

Cigarettes are the most common form of tobacco worldwide. Various form of smoking tobacco are cigar, beedis and cigarettes. *Beedis* which are consisting of tobacco flakes wrapped in temburni

leaf with a little thread at one end are very popular in India. The puff` rate of beedi is higher than that of an unfiltered cigarette which is the reason for the increased carcinogenic load of *beedis.*

Nicotine is the major central nervous system stimulant present in tobacco. It increases the available dopamine in nucleus and causes mood elevation and causing addiction. Major carcinogens in tobacco causing cancer are polycyclic aromatic hydrocarbons, NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] and NNN (N1-nitroso nor nicotine).

SMOKELESS TOBACCO

Worldwide there is increase in use of other nicotine deliverance like snuff, lozenges,betel quid. Betel quid is widely used in India. It is also called as *pan* which contains pieces of areca nut, tobacco and slaked lime. Additional to this are spice, cardamom, cloves, according to their need. Pan also called as *gutkha, zarda, mawa, khaini.*

Irritable substance in the Areca nut is notorious to cause **oral submucous fibrosis**. Smokeless tobacco is not an equal form to compare smoking tobacco. Definitely the content of nicotine and the carcinogens are many times increased in smokeless tobacco.

ALCOHOL

Tobacco and alcohol combined that increases the risk of developing head and neck cancer many fold. Both of it acts synergistically. Alcohol is a predictor of survival [4]. Prognosis for alcoholic head and neck cancer patients is not as good as when compare the non alcoholic patients. Because most of them have advanced disease at presentation, suppressive immune status, diseases attributed to alcohol consumption, harmful nutritional habits, and emotional disturbances.

HUMAN PAPILLOMA VIRUS INFECTION:

Most of the oropharyngeal cancers associated with HPV infection. Most common human papilloma virus inked is HPV 16. Main route of spread is through oral sex. 30-40% of oropharyngeal cancers, 24% of oral cavity carcinoma were associated with HPV. Other common subtypes are HPV 18 and 31.

OTHER CAUSES

Other causes are iron deficiency (Plummer Vinson Syndrome), vitamin A deficiency, sharp tooth and occupational exposure like asbestos, nickel, chromium, by product of leather work and wood working [17].

More than half of the patients presented with locally advanced disease in our department. Ninety five percent are squamous cell carcinoma. Rest of the five percent includes verrucous carcinoma, minor salivary gland tumors, melanomas, adeno carcinoma, lympho epitheliomas, and lymphoma.

Oral cavity ulceration, bleeding from the mouth ,sore throat, dysphagia, hoarseness of voice, earache, pain, numbness of the face, dyspnoea, difficulty in speech or inability to open the mouth and headache are the common symptoms during presentation.

The work up include a thorough history and physical examination. Then clinical examination of the primary with fiber optic endoscope, biopsy, chest imaging, CT or MRI imaging of the tumor and neck, blood investigations and dental care.

OVERVIEW OF TREATMENT OF SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

Multimodality treatment approach for head and neck cancers at present practiced are

1) Surgical excision followed by adjuvant radiotherapy with or without chemotherapy

2) Definitive chemo radiotherapy followed by surgery as salvage.

3) Induction chemotherapy followed by definitive loco regional therapy.

SURGERY

Surgery is a part of the multimodality treatment approach. It has evolved in the recent years owing to outstanding reconstruction procedures. Robotic microsurgical techniques, imaging modalities and surgical pathology also advances. Surgical resection is classified as-***resectable, unresectable and inoperable.***

RESECTABLE

Surgical feasibility of a head and neck cancer is assessed by a multidisciplinary team. The excision of advanced cancers of oral cavity, pharynx and larynx is by an en bloc resection to gain adequate resected margins.

An *adequate margin* when the clearance is about **1.5 cm to 2cm** in frozen section. A *clear margin* is as a distance of ≥ **5 mm** from the resected margin to the invasive tumor. A *close margin* is a distance of < **5 mm**. Resection is usually through a transoral, transcervical approach or, through mandibular excision.

Reconstruction of surgical area by primary closure, skin graft, regional flap or a free tissue transfer. Reconstructed area should functionally and anatomically look like the normal tissue.

NECK DISSECTION

Elective neck dissection should be performed in clinically negative nodal disease in neck. Curative neck dissection should be done in patients with clinical evident of node positive disease. Based on the clinical, imaging and preoperative finding, therapeutic dissections is either *selective neck dissection* or a *comprehensive neck dissection*. Tumors crossing midline or primary with bilateral lymphatic drainage should undergo bilateral neck dissection.

UNRESECTABLE

Carcinoma is considered unresectable by the surgeon if the tumors could not be excised to give an adequate margin. Not only margin, local and regional control even after postoperative chemo radiotherapy to the treatment. When surgical procedure produces unacceptable morbidity, then patients can go with definitive radiotherapy or chemo radiotherapy with the same outcome as that of surgery.

INOPERABLE

Constitutional state of the patient precludes surgery. The tumor may be resectable with least morbidity.

SALVAGE SURGERY

Patients with advanced head and neck cancer treated with, definitive radiatherapy or chemo radiatherapy, may have residual disease or with recurrence in the primary site or nodal site. So they should be monitored periodically. They should undergo salvage surgery if there is a residual or recurrent disease. The complication rates after salvage surgery is more when compared with upfront surgery.

RADIOTHERAPY

Primary and macroscopic nodal disease are to be treated with 66 to 74 Gy in conventional 2 Gy fractions. Low to intermediate risk of lymphadenopathy to be treated electively between 44 and 64 Gy. Advanced T stage, depth of invasion, perineural invasion, multiple positive nodes, lymphovascular invasion requires postoperative radiotherapy. Extra capsular extension and positive margins are indication for post operative chemoradiation. Postoperative radiotherapy is administered between 4 and 6 weeks after surgery. Radiotherapy may be conventional or altered fractionation.

ALTERED FRACTIONATION

ACCELERATED RADIOTHERAPY

The overall treatment time is reduced. So tumor cells regeneration is less during the treatment. Hence better local and regional control is achieved.

Pure accelerated radiotherapy:

Here the overall treatment time is reduced but no change in the total dose or fraction size.

Hybrid accelerated fractionation: There are three types.

Type A: Drastic reduction in overall treatment time and also considerable reduction in the total dose.

Type B: Treatment time is reduced, total dose remains the same with an additional break in between treatment.

Type C: Total dose is same; overall treatment time is decreased with an addition of a concomitant boost phase (Accelerated concomitant boost).

HYPER FRACTIONATED RADIOTHERAPY

In hyper fractionated radiation therapy, total dose of radiation is increased, dose per fraction is significantly reduced, the numbers

of fractions are increased and overall treatment time is significantly unchanged.

CHEMOTHERAPY

Benefits of chemoradiation are independent cytotoxicity of each of the modality, spatial cooperation, enhancement of tumour response by radio sensitisation and tackling of the systemic micro metastasis.

RADIOTHERAPY AND CHEMOTHERAPY INTERACTION MECHANISMS

INCREASING INITIAL RADIATION DAMAGE:

Chemotherapy increases the initial DNA damage by single stranded and double stranded DNA breaks, base damage ,DNA-DNA and DNA protein cross links.

INHIBITION OF CELL

Both sub lethal and potentially lethal damage produced by radiation can be repaired. Chemotherapy drugs interfere with DNA repair mechanisms and increase response to radiotherapy.

CELL CYCLE REDISTRIBUTION

The G2M phase of cell cycle is three times more susceptible to radiation than S phase. Chemotherapy drugs like taxol block progression of cell cycle in the transition through mitosis phase and

all cells accumulate in the G2M phase. So when taxol is added to radiotherapy there is an enhanced tumour kill.

OVERCOMING TUMOR HYPOXIA

Radiotherapy and chemotherapy preferentially kill the actively proliferating cells in the oxic regions of the tumour. With each dose of radiosensitiser chemotherapeutic drug and radiation, the well oxygenated cells in the periphery of tumour die. There is a gross fall in the interstitial pressure within the tumour causing opening up of previously closed capillaries and redirection of blood to the hypoxic regions of the tumour.

INHIBITION OF TUMOR CELL REPOPULATION

Chemotherapy is both tumoricidal and tumoristatic. By using a combination there is a hastened killing of tumour cells and reduction in the rate of treatment related accelerated repopulation of cancer.

The current study protocol takes the benefit of hyper fractionated radiotherapy and concurrent usage of chemotherapeutic sensitizers namely docetaxel .

DOCETAXEL

Classified as a Anti-microtubule agent

MECHANISM OF ACTION

It is active in the Mitosis (M) phase of the cell cycle and has a high-affinity towards microtubules and enhances tubulin polymerization. The tubulin thus formed are resistant to disassembly by normal physiological process and they accumulate as disorganised array [13]. Docetaxel is more effective at inducing apoptosis and inhibiting anchorage-independent cell growth .[23]

MECHANISM OF RESISTANCE

Alterations in tubulin, increased expression of P 170 glycoprotein resulting in enhanced drug efflux and decreased intracellular accumulation of drug causes resistance to the drug.

The drug is poorly soluble and not orally bio available.

It is widely distributed to all body tissues and excessively protein bound.

Metabolised by hepatic P 450 enzyme. 70% to 80% are excreted by faecal route with a terminal half life ranging from 9 to 50 hours. Cross resistance also will occur with other products like Vinca alkaloids,Anthracyclines and Etoposide.

Docetaxel is indicated in a broad range of cancers like ovary, breast, lung, head and neck, oesophagus, prostate, bladder and

AIDS-related Kaposi's sarcoma. Myelosuppresion is a dose limiting toxicity. Neutropenia is more common with a nadir at 8 days and recovery between day 15 and 21; hypersensitivity is prone to occur in 20% to 40% patients. Also peripheral neuropathy, mucositis, diarrhoea and alopecia may occur.

SUMMARY OF MECHANISMS OF INTERACTION BETWEEN HYPER FRACTIONATED RADIOTHERAPY WITH DOCETAXEL

REPAIR OF SUBLETHAL DAMAGE

Hyperfractionated radiotherapy with an inter fraction interval of not less than 6 hours allows repair of ***sublethal damage repair*** in normal tissues. In twice daily fractionation, an absolute minimum interfraction interval of 6 hours was advocated by ***EORTC 22791 and 22851***. So ***dose escalation*** is possible without increasing the late toxicities.

REDISTRIBUTION OF THE CELL CYCLE

Docetaxel accumulates the cells in the G2M phase and increases the number of cells in the ***radiosensitive phase***. So cell killing is enhanced in the next hyperfractionated dose.

REPOPULATION

Increased and effective killing of cells right from day 1 of radiation decreases both the tumor bulk and ***repopulation*** steadily**.**

REOXYGENATION

Oxygen enhancement ratio is lower.

THERAPEUTIC INDEX

It is defined as the ratio of the tumor response to a fixed level of normal tissue damage. To be therapeutically beneficial, the ratio should be greater than 1. There is a precarious balance between the antitumor activity and the normal tumour tissue toxicity. Many clinical parameters like a palliative or a curative choice of treatment, dose limiting structures, amount of toxicity acceptable, and the individual patient's radio sensitivity influence the therapeutic ratio.

EXPLOITABLE STRATEGIES IN CHEMORADIATION:

Radiation has attained a pinnacle of improvement in various avenues like technological advances, combination treatment with chemotherapy altered fractionation schedules, biological agents, targeted agents and hypoxic cell sensitizers. All these modalities have to be explored to generate optimum treatment schedules.

RADIOBIOLOGICAL RATIONALE FOR HYPERFRACTIONATION

Smaller dose fraction allows a higher total dose to be executed well within the tolerance of late responding normal

tissues. Higher total dose translates into a higher biological effective dose. Other rationales are radio sensitization through redistribution and lesser dependence on oxygen effect. More the number of fractions, greater are the chances that the tumour cells would be in radiosensitive phase in the next fraction.

So our intent of using concurrent chemotherapy added to hyperfractionation in the treatment of advanced unresectable Head and Neck squamous cell malignancies is to preserve organ function and to maximize local tumor control. This enhanced control is expected to translate as a survival benefit as evidenced from a number of previous studies.

Careful patient selection, monitoring of the patient's general condition and emotional balance throughout the treatment enable better compliance to treatment completion. Patients' motivation to undergo the six week journey of chemo radiation along with proper counseling and disease education are very crucial.

REVIEW OF LITERATURE

COMPARISION OF HYPERFRACTIONATED RADIOTHERAPY TO CONVENTIONAL RADIOTHERAPY

Hyperfractionation has been extensively studied in varied setting like head and neck cancers, bladder cancer, lung cancer, rhabdomyosarcoma, whole brain radiotherapy for brain metastasis and acute lymphoblastic leukemia. But most striking results were obtained from head and neck malignancies.

By addition of chemotherapeutic agents better radiosensitisation is aimed at and it directly manifests as improved oncological outcome. Dose escalation is achieved at the cost of increased acute toxicities.

As early as in **1978**, the results of **RTOG 77-03** by Marks R [31] concluded that hyperfractionated radiotherapy (66 Gy in 1.25 Gy BID) gave adequate tumor control, with acceptable acute and late toxicity. Dose greater than 1.5 Gy BID was too toxic, and required treatment breaks.

In **1987**, Marcial *et al* [34] reported the results of **RTOG 79-13** (1979-1983). The study randomized 187 patients of Stage III-IV or T2N0 base of tongue, nasopharynx, and maxillary sinus to receive

either conventional radiotherapy 66 Gy to 73.8 Gy in 1.8-2 Gy/fraction once daily or hyperfractionated radiotherapy 60 Gy in 1.2 Gy BID, 3-6 hrs apart. The 2 year locoregional control rate with conventional radiotherapy was 29% and with hyperfractionated radiotherapy was 30% (not statistically significant).More acute reactions were reported from hyperfractionated radiotherapy arm. Late reactions were similar between the two arms.

In **1992**, **Horiot *et al*** [24]analyzed the **EORTC 22791** [35] (1980-1987) study results of 356 oropharyngeal cancers of stage T2- N0-1 (base of tongue and size < 3 cm lesions were excluded).The patients were randomized to receive either conventional radiotherapy 70 Gy in 7-8 weeks or pure hyperfractionated radiotherapy 80.5 Gy in 1.15 Gy fractionation twice daily. Hyperfractionation arm showed a higher local disease free survival (59%) compared to conventional fractionation (40%). Hyperfractionation arm also showed an improvement in overall survival (p=0.08) .T3 tumors especially responded well to hyperfractionation. No difference was observed in late effects.

In **1993**,**Parson *et al*** [32] from University of Florida showed a improved locoregional control for 419 patients of T2 to T4

squamous cell carcinoma of the head and neck treated with twice-a-day radiotherapy (1.2 Gy BID to 74.4 -79.2 Gy).

PHASE III TRIALS OF HYPERFRACTIONATED RADIOTHERAPY

Outcomes	Study arms	Pinto et al[25]	Fu et al [26] (2000)	Cummings et al(2000)
Dose/fraction	Arm 1	1.1 Gy BD	1.2 Gy BD	1.45 Gy BD
	Arm 2	2 Gy OD	2 Gy OD	2.55 Gy OD
Total dose	Arm 1	70.4 Gy	81.6 Gy	58 Gy
	Arm 2	66 Gy	72 Gy	51 Gy
Overall time	Arm 1	6.5 weeks	6 weeks	4 weeks
	Arm 2	6.5 weeks	7 weeks	4 weeks
LCR	Arm 1	84%	Higher in Hyper fractionation arm P=0.04)	45%
	Arm 2	64% (p=0.02)		37% (p=0.01)
Overall survival rate	Arm 1	27%(3 yr)	No Difference In OS	40%(5 yr)
	Arm 2	8 %(p=0.03)		30% (p=0.01)
Side effects		Early acute reactions	More mucositis with HF, No difference in late complication rate.	

All the following trials say hyper fractionated radiotherapy is better when compared to conventional fractionation.

COMPARISION STUDY OF HYPERFRACTIONATED RADIOTHERAPY WITH OTHER ALTERED FRACTIONATION SCHEDULES

Between **1991 to 1997** ,a phase III randomized study **RTOG 90-03** [38] compared standard fractionation, hyperfractionation, split course accelerated fractionation and accelerated fractionation with concomitant boost. 1073 patients of Stage III-IV (oral cavity, oropharynx, or supraglottic larynx) or Stage II-IV (base of tongue, hypopharynx) were randomized into 4 arms.

Arm 1. Conventional fractionation 70 Gy in 35 fractions (2 Gy/fraction)

Arm 2. Hyperfractionation 81.6 Gy in 68 fractions (1.2 Gy BID)

Arm 3. Split course accelerated fractionation 67.2 Gy in 42 fractions (1.6 Gy BID) with 2 week break after 38.4 Gy

Arm 4. Concomitant boost 72 Gy given 54 Gy in 30 fractions (1.8 Gy OD) + 18 Gy in 12 fractions (1.5 Gy concurrent BID boost)

There were increased acute effects but no increase in late effects. So he concluded that hyperfractionation or Concomitant Boost improved locoregional control when compared to standard fractionation.

RESULTS OF RTOG 90-03

outcomes	Standard fractionation	Hyper fractionation	Accelerated fractionation with split course	Accelerated concomitant boost
2 Year DFS	32%	38%	33%	39%
5 Year DFS	21.2%	30.7%	26.6%	28.9%
2 Year OS	46%	54%	46%	51%
5year OS	29.5%	37.1%	30.8%	33.5%
Local Failure	44%	38%	43%	37%
Regional Failure	32%	27%	31%	33%

DFS-disease free survival; OS-overall survival

There was no impact on disease free survival and overall survival. Split course was comparable to standard fractionation. In 2005, **Trotti** [33] reported the 5 year follow up in ASTRO. He showed a trend for increase in grade 3+ late effects with AFX-CB (p=0.066).TWIST analysis done in the RTOG study group in 2008 showed quality adjusted survival was better only for hyperfractionation and not for accelerated fractionation.

IMPACT OF NUTRITION

In **2006**, Rabinovitch [36] did a secondary analysis on the impact of nutrition in the **RTOG 90-03** patients. Patients who were in nutritional support even before treatment attained inferior outcomes.

RTOG 83-13 studied dose escalation with hyperfractionation between 1983 and 1987 in a phase II randomized trial. 451 patients of advanced head and neck cancer were treated with hyperfractionation 1.2 Gy BID, 4 hrs apart, up to 67.2 Gy; 72.0 Gy and 76.8 Gy in each arm.

2-year locoregional control showed improvement with dose escalation [25% vs. 37% vs. 42% (p=0.08)] 2-year Grade 4 necrosis reported was 10% vs. 5% vs. 14% respectively.

5 year follow up of **RTOG 83-13** reported that there is no difference in late toxicity between the dose escalated hyperfractionation groups and that the ideal interfractionation interval should be >4.5 hours.

In **1986**, **EORTC 22811** compared hyperfractionation with or without hypoxic cell sensitisers like misonidazole with

conventional radiotherapy . There was no difference in survival or local control with addition of misonidazole.

CONCURRENT CHEMOTHERAPY IN ADDING UP HYPER FRACTIONATED RADIOTHERAPY

SINGLE AGENT CHEMOTHERAPY

A low dose of cisplatin was added to hyperfractionation by **Denham *et al***. Various sites and stage III – IV cancers were treated.

- **Arm 1**: 77 Gy/7 wk + Cisplatin (6 mg/m^2/d)
- **Arm 2:** 77 Gy/7 wk (1.1 Gy, bd.)

5-year Progression Free Survival: 46% vs. 25% (p = 0.007); 5-year Distant Metastasis Free Survival: 86% vs. 57% (p = 0.001) and 5-year Overall Survival: 46% vs. 25%. (p = 0.008). There were no significant difference in acute toxicities (except for leucopenia, p = 0.006) or late toxicity.

In **2000, Jeremic *et al***. [14] conducted a randomized trial in hyper fractionation with chemotherapy in 130 stage III and IV patients and found improvement in all oncological outcomes .This was a true therapeutic gain because there was no difference in late side effects. Results are as tabulated.

RESULTS OF HYPER FRACTIONATION WITH CHEMOTHERAPY JEREMIC *ET AL*

Outcomes	HFX with Chemo (low-dose daily cisplatin + 77 Gy /1.1 Gy / fraction BD)	HFX 77 Gy / 1.1 Gy / fraction twice daily
LRC	50%	36%; P=0.04
5-year PFS	46%	25%; P=0.007
5-year DMFS	86%	57%; p = 0.001
5-year OS	46%	25%; p = 0.008

HFX-HyperFractionation; LRC-LocoRegionalControl; PFS-Progression Free Survival; DMFS-Distant Metastasis Free Survival; OS-Overall Survival

Also there is a report from ***Zurich*** which randomized 224 patients with squamous cell carcinoma as follows:

Arm-1: 2 cycles of Cisplatin 20 mg/m^2 on 5 days of weeks 1 and 5 + Hyperfractionated radiotherapy (74.4 Gy in 1.2 Gy twice daily)

Arm2: Hyperfractionation 74.4 Gy in 1.2 Gy twice daily only.

Loco regional control (p=0.039) and distant disease-free survival (p = 0.011) were significantly improved with concurrent Cisplatin with hyper fractionation. There was no difference in overall survival and similar late toxicity.

In **2004**, **Heguenin P *et al***, [30] (Swiss trial) randomized advanced head and neck cancer patients to hyperfractionated radiotherapy 1.2 Gy twice daily up to 74.4 Gy with or without 2 cycles of concurrent Cisplatin 20 mg/m^2 on days 1 to 5 of weeks 1 and 5. He reported an improvement in the locoregional control rate and distant disease free survival but there was no difference in overall survival.

MULTI AGENT MODALITY CHEMOTHERAPY CONCURRENT WITH HYPERFRACTIONATION

German Cancer Society compared hyper fractionated accelerated radiotherapy with concurrent chemotherapy with dose escalated hyperfractionated accelerated radiation. 84 patients with stage III and IV head and neck cancer were randomized.

Arm-1: Concurrent chemotherapy and Hyper fractionated accelerated radiotherapy to 70.6 Gy in 6 weeks

Arm-2: Hyperfractionated accelerated radiation alone to 77.6 Gy

CHEMOTHERAPY

5-fluoroucil (600 mg/m^2IV continuous infusion for 120 hours) on days 1-5 and Mitomycin (10 mg/m^2) on days 5, 36.

GERMAN CANCER SOCIETY TRIAL RESULTS

Disease outcomes	Hyper fractionation with chemotherapy	Hyper fractionation alone
5 yr loco regional control	49.9%	37.4% (p = 0.001)
5 yr overall survival	28.6%	23.7% (p=0.023)
Progression-free rate	29.3%	26.6% (p = 0.009)
freedom from metastases rates	51.9%	54.7% (p = 0.575)

There were no differences in late reactions.

Brizel *et al* [29] compared hyperfractionated radiotherapy alone 75 Gy in 60 twice daily fractionation with hyperfractionated radiotherapy (70 Gy in 56 twice daily fractions with a 7 day split in between) with concurrent chemotherapy. 2 cycles of concurrent Cisplatin 12 mg/m2 and 5 FU 600 mg /m2 day 1 to 5 was given concurrently with radiation and 2 more cycles of the same chemotherapy was used as maintenance.

BRIZEL ET AL STUDY RESULTS OF HYPERFRACTIONATED RADIOTHERAPY AND CHEMOTHERAPY

Outcomes	Hyperfractionation alone	Hyperfractionation and CDDP+5FU
3 YEAR LOCOREGIONAL CONTROL RATE	40%	70% (p=0.01)
RELAPSE FREE SURVIVAL RATE	41%	61% (p=0.08)
OVERALL SURVIVAL RATE	34%	55% (p=0.07)

RESULTS OF METAANALYSIS OF HYPERFRACTIONATED CHEMORADIOTHERAPY

In Sept 2006 ***MARCH Collaborative group***, reported the results of a meta-analysis of head and neck cancers patients treated with chemoradiotherapy. A total of 15 trials were analyzed .Study population included 6515 patients. A median follow up 6 years was done. Oropharynx and larynx cancers were most common subsites treated.74% of the study population belonged to stage III and IV. The analysis showed an overall survival benefit with altered fractionation schedules. An absolute benefit 3.4% at 5 years; HR= 0.92, 95% CI 0.86-0.97,p=0.003 was observed.

There was a significantly higher benefit with hyper fractionation 8% at 5 years. Locoregional control with altered fractionation was better than conventional radiation 6.4% at 5

years ($p<0.0001$). Benefit observed was less in older patients aged > 70 years.

In the meta analysis conducted by **Budach *et al*** [19]combined chemotherapy with altered fractionation was studied. 32 trials were studied and 10225 patients were analyzed. Overall survival benefit of 12 months was observed with addition of chemotherapy to conventional/ altered fractionation ($p<0.001$). There was a substantial prolongation of median survival of 14.2months with hyperfractionation compared to conventional RT.

In 2007, ***Bourhis et al*** [27]analyzed 120 randomised trials comprising of 25,000 patients. A median follow up to 6years was done. He reported that an addition of chemotherapy to hyper fractionation and accelerated fractionation regime improved locoregional control and survival outcome compared with only radiation. Other reported acute toxicities and long term toxicities were comparable.

They concluded that concurrent chemotherapy with Hyper fractionated accelerated radiotherapy to 70.6 Gy was superior to dose-escalated hyperfractionated radiotherapy to 77.6 Gy with less acute reactions and equivalent late reactions.

The MACH-NC meta-analysis says for patients who undergo a non surgical treatment, concurrent chemoradiation is the standard. The UKHAN 1 trial also confirms this. The UKHAN 1[21] study also says long term benefit in terms of reduced recurrence and deaths can be achieved with non – platinum agents.

So using hyperfractionated radiotherapy with a chemotherapy a non platinum agent (Docetaxel) is a novel protocol to treat the unfavourable locally advanced and unresectable squamous cell carcinomas of head and neck.

CONCURRENT CHEMOTHERAPY DOCETAXEL WITH HYPERFRACTIONATION

Karasawa et al studied hyperfractioned radiotherapy with Docetaxel in 70 patients treated with 1.2gy per fraction. Oropharynx 25, hypopharynx 2, larynx 18 an other sites 3 were studied. Median follow up was 43 months and 5 year local control rate = 62.6%,Over all survival rate 61.6% with acceptable toxicity.

Fumihiko et al had studied and analysed in 25 patients of locally advanced head and neck carcinoma treated with hyperfractionated radiotherapy and weekly docetaxel shows complete response in the primary is 84%,complete response in secondary is 61% and the overall response rate is 68% with minimal toxicities.

AIM OF THE STUDY

To assess the immediate loco regional response rates of locally advanced unresectable squamous cell carcinomas of the head and neck treated with hyperfractionated radiotherapy and concurrent weekly Docetaxel

OBJECTIVE(S)

- To assess acute toxicity to the treatment.
- To assess the prognostic factors which determine the response to treatment.

MATERIALS AND METHODS

TYPE OF THE STUDY

Cross Sectional Study

DURATION

March 2015to September 2015

NUMBER OF PATIENTS

30

PATIENT INFORMED CONSENT

All patients were given an information sheet detailing the full course of the study protocol. Informed consent was obtained from them in the local language (Tamil) which was specially made to serve the purpose. Hand outs explaining the do's and dont's during radiotherapy with explanations about the oral care, dental care, skin care and nutritional care were made available to them. Institutional ethical committee clearance was obtained.

PATIENT SELECTION

Patients with stage III and IV unresectable squamous cell carcinoma of head and neck were treated in this protocol.

INCLUSION CRITERIA

- Biopsy proven newly diagnosed squamous cell carcinoma of the head & neck.
- Tumours considered unresectable due to technical inability to obtain a clear margins.
- Primary tumor sites: oral cavity, oropharynx, hypo pharynx, larynx.
- Age >18 - 60 years
- Stage III or IV (M0) nonmetastatic disease (AJCC staging manual 7th edition)
- Previously untreated for the present malignancy
- No prior history of cancer
- No prior exposure to radiotherapy or chemotherapy
- KPS>/=70%
- No major life threatening co morbidities.

EXCLUSION CRITERIA

- Non Squamous Histopathology

- Tumours of nasal cavity, paranasal sinuses, nasopharynx and salivary gland .
- Primary involving bone/cartilage
- Recurrent tumours
- Inadequate hepatic and renal functions, bone marrow reserve.
- Patient not consenting to chemotherapy at any point in the treatment.
- Previously received treatment for any other malignancy (within past 5 yrs)
- Pregnant females.

WORK UP

- Complete history and physical examination
- Biopsy from tumour

BLOOD INVETIGATIONS

- Complete blood count WBC > 4000 /mm^3
- Haemoglobin >11%
- Platelet count >1, 00,000/cu mm

- Serum Creatinine </=1.2mg/dl
- Liver function tests: Serum Total Bilirubin </=1.2mg/dl
- Blood Grouping and Typing

RADIOLOGICAL IMAGING

CT scan Neck (From base of skull to Root of Neck) – Plain and Contrast pre-treatment and post treatment).

- Pan Endoscopy
- Cardiac evaluation: ECHO cardiogram, ECG, chest X-ray
- Weekly CBC, RFT before each course of chemotherapy
- Staging is done based on American Joint Committee staging manual 7^{th} edition (for head and neck cancers).

PRETREATMENT PATIENT PREPARATION

ORAL CARE

Mucositis is the most important therapy limiting toxicity in head and neck cancer treatment. An indigenously prepared solution by dissolving three tablespoons of soda bicarbonate and three tablespoons of table salt (sodium chloride) in 1 gallon of distilled water was used for mouth gargle. Patients were asked to gargle ten times a day, especially after food. Patients who developed oral

candidiasis were treated with tablet Fluconazole 100 mg po or Clotrimazole lozenges for 7 days.

DENTAL CARE

Prior to starting chemo radiation a thorough oral and dental evaluation was done in all eligible patients. Following dental prophylaxis a rest time of 2 weeks was given for proper healing of the gums over the extracted tooth and for any associated infection to subside.

Advanced carries, tooth in a state of disrepair were extracted to minimize the risk of osteo radionecrosis. Impacted tooth may also be considered for extraction. Marginal tooth may be extracted to enable patients to maintain a good oral hygiene and better nutrition.

Nature of salivary secretions is altered due to irradiation of major and minor salivary glands. This reduces the buffering ability and pH of saliva and enhances debris and plaque formation over the tooth .Radiation itself causes hypocalcification of tooth. So daily cleaning with a fluoride containing toothpaste, flossing, and soft brushing were done during and after radiotherapy.

NUTRITIONAL SUPPORT

Treatment related weight loss is known to occur in head and neck chemoradiation due to the disease per se or treatment related toxicities. Nutritional interventions like nasogastric tubes, percutaneous endoscopic gastrostomy tubes and intravenous nutritional support were offered to patients for whom enteral feeding was not feasible to combat the caloric requirements.

The NCCN 2012 panel does not recommend prophylactic nasogastric tube or gastrostomy tube placement for patients in good performance status without pretreatment weight loss, severe airway obstruction or dysphagia.

SMOKING CESSATION

Elevated interest to quit smoking was used an opportunity to intervene and provide assistance in the quitting process.

A proposed mechanism of biological interaction of radiation and smoking by Grau et al hypothesize that the hypoxia caused by high levels of carboxyheamoglobin in smokers correlate with the poor oncological outcome.

Nicotine also interferes with the chemotherapeutic efficacy by inducing resistance to chemotherapy induced apoptosis by

modulating the mitochondrial signaling. Treatment related adverse side effects like mucositis, xerostomia, poor voice quality, disfigurement are higher in patients who continue to smoke.

MULTIDISCIPLINARY TEAM

All patients had access to full range of specialists and support services with expertise in the management of head and neck cancers for optimal treatment and follow up. Specialized nursing care, speech and swallowing therapy, nutrition support, psychiatry, deaddiction services, audiology and palliative care were made available.

TREATMENT

All patients were treated as inpatients to enable them to receive the twice daily radiation and six weekly chemotherapy cycles.

PROTOCOL

30 patients with locally advanced unresectable squamous cell carcinomas of the head and neck satisfying the inclusion criteria after completion of the pretreatment work up and preparation as mentioned earlier were treated with hyperfractionated radiotherapy and weekly docetaxel .

RADIOTHERAPY PLANNING

A total planned dose of **72 Gy** was delivered in **120 cGy per fraction; two fractions per day at 6 hours interval,** to the selected treatment fields. Patients received radiation **5 days a week** and chemotherapy was given in between the two radiation fractions. Radiation was given using a **cobalt 60 Theratron Phoenix** machine at 80 cm SSD.

RADIATION DOSAGE

Patients were treated from Monday to Friday of the week. Each day they receive 120 cGy twice so that they achieve 2.4 Gy per day. Similarly they receive radiation for 6 weeks. Hyperfractionated radiotherapy treatment was complete by 6 weeks. Dose received per week is 12 Gy as opposed to conventional radiotherapy where the dose is 10 Gy per week.

RADIATIONFIELDS

Initial treatment field included the primary tumor plus 2 cm margin, clinically involved secondary lymph nodes and the lymph nodes probable to lodge the occult microscopic disease in the drainage area. Uninvolved lymph nodal stations received 50.4 Gy (21 fractions) while the clinically involved nodes proceed up to the

final dose as for the primary. Dose was calculated in the midplane for opposing lateral fields.

RADIATION PORTALS

All patients were treated with opposed lateral fields and appropriate shielding of the spinal cord was done after 45 Gy as per the institutional policy.

VERIFICATION

All treated patients were placed in treatment position and simulated. The treatment portals were verified and corrections were made.

DOSE CONSTRAINTS

Tolerance dose of spinal cord is 45 Gy in conventional fractionation for a length of 5 to 10 cm. Parotid is tolerant up to 26 Gy after which permanent xerostomia is expected to occur.

CHEMOTHERAPY

Injection docetaxel 20 mg /m ^{2}was given on every Monday, weekly for a total of 6 courses inbetween the two fractions.

PREMEDICATION

Pre hydration with one litre of normal saline is done for two hours.

Premedication given 30 minutes before chemotherapy is as follows

- Injection Ranitidine 50 mg IV
- Injection Dexamethasone 20 mg 12 hr, 6 hr and immediately (30 minutes) before administration of docetaxel
- Injection Pheneramine maleate 45.5 mg IV
- Injection Ondansetron 8 mg IV

Injection docetaxel 20 mg /m^2 is mixed in 500 ml of normal saline and infused in intravenous codon set with extravasation precautions. Following this 500ml of normal saline is again infused for one hour.

Every week blood investigations were repeated before chemotherapy. Any fall in blood parameter like haemoglobin was corrected by blood transfusion; colony stimulating factor was proposed to be used when the Absolute Neutrophil Count[ANC = (segmented neutrophils% + segmented bands%)/ 100 x WBC count in multiples of 1000s] would fall below 1000 cells/cubic millimetre and only symptomatic thrombocytopenia was corrected by platelet transfusion. Entire treatment is to be completed in 6 to 7 weeks ideally.

PATIENT CARE DURING CHEMORADIATION

TOXICITY ASSESSMENT

Patients are reviewed every day before radiation. Firstly, attention was given to the maintenance of a good oral hygiene. Good hydration status of the patient was ensured. Local toxic reactions like epilation, skin reactions, dysphagia, laryngitis, xerostomia and mucositis were recorded and graded. Radiation was suspended once patient developed grade 3 or above acute reactions. Also adequacy of the daily calorific value of food was ensured.

Hematological parameters were looked into every week before the weekly dose of chemotherapy. Any level of haemoglobin less than 10 gm/dl was corrected by packed red cell transfusion. WBC and platelet counts were also checked.

RESPONSE EVALUATION

Patients were reassessed with CT Neck 4 -6 weeks after completing chemo radiation.

- Tumor response as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria

- ***Complete Response:*** Disappearance of all target lesions; malignant nodes <10 mm.

- ***Partial Response:*** At least 50% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; confirmed at 4 weeks.

- ***Stable Disease:*** Neither partial response nor progressive disease criteria are met, in a minimum time set by the protocol

- ***Progressive Disease:*** At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5 mm, taking as reference the smallest sum in the study or appearance of new lesions.

FOLLOW UP

Patients were discharged a week after completion of chemoradiotherapy or complete recuperation whichever is earlier.

They were reviewed with a CT neck plain and contrast 4weeks after completion of chemoradiotherapy for response assessment. Response evaluation was done using RECIST criteria as mentioned above.

Chest imaging, dental evaluation, hearing evaluation were done as clinically indicated. Continued smoking cessation, rehabilitation, speech and swallowing therapy were offered.

RESULTS

30 patients who satisfied the inclusion criteria were accrued to the study from March 2015 to September 2015.Patients underwent treatment as per protocol. 30 patients completed the planned course of chemotherapy and radiotherapy.

PATIENT CHARACTERISTICS

1.Age Distribution

30 patients were enrolled into the study.

Table 5.1.Age Distribution

Age Group	No. of Patients	Percentage (%)
11 to 20 years	0	0
21 to 30 years	0	0
31 to 40 years	7	23.33%
41 to 50 years	15	50%
51 to 60 years	8	26.66%

Median age of the study population is 45.03 years. Age groups ranged from 31 to 59 years.50% of the study population were between 41 to 50 years of age group.

2.GENDER

Male patients outnumbered females.28 of the study population were male and 2 were female.

Table-5.2: Gender Distribution

Gender	No. Of patients	Percentage (%)
Male	28	93.33%
Female	2	6.66%

3. KARNOFSKY PERFORMANCE STATUS:

Hyperfractionation with chemotherapy is a challenging treatment protocol which mandates good performance status. 70%patients were in KPS score of 90; 13.33% patients were in performance score 80 and 16.66% patients in score 70.

Table 5.3.Karnofsky Performance Status

SCORE	NO. OF PATIENTS	PERCENTAGE (%)
90	21	70%
80	4	13.33%
70	5	16.66%

4. HABITS:

33.33% of the study population used smokeless tobacco and alcohol; 26.66% used smoking forms of tobacco and alcohol;6.67 % had smoking habit only; 10% used smokeless tobacco only; 10% used alcohol only and 13.33% had all three habits.

17 patients (56.66%) used smokeless tobacco either alone or in combination with smoking and alcoholism .This high incidence of smokeless tobacco usage is associated mostly with oral cavity cancers which constitutes a third of our study population.

Table 5.4.Habits

Habits	No. Of patients	Percentage (%)
Smoking+smokeless tobacco usage+alcoholism	4	13.33%
Smoking and smokeless tobacco usage	0	0
Smoking and alcoholism	8	26.66%
Smokless tobacco use+alcoholism	10	33.33%
Smoking only	2	6.67%
Smokeless tobacco use only	3	10%
Alcoholism only	3	10%

5. SUBSITE DISTRIBUTION:

Most of patients had primary in oropharynx (40%) and oral cavity (36.66%) followed by larynx (20%) and then hypopharynx (3.33%). One patient each in the oral cavity (T3 N3) group and the oropharyngeal group (T4a N3) could not complete the planned treatment.

Table 5.5 Subsite Distribution

Subsite	No. Of patients	Percentage
Cancer oral cavity	11	36.66%
Cancer oropharynx	12	40%
Cancer hypopharynx	1	3.33%
Cancer larynx	6	20%

6. PRIMARY TUMOR CHARACTERISTICS

66.66% patients had in T3 tumors and 33.33% had T4a tumors. None of the patients had T4b tumor.

Table 5.6 Primary Tumor Characteristics

T stage	No. Of patients	Percentage
T3	20	66.66%
T4a	10	33.33%
T4b	0	0

7. SECONDARY NODE CHARACTERISTICS

20% patients had N0, 33.33% patients had N1 nodes, 40% patients had N2 nodes and 6.67% patients had N3 nodes.

Table 5.7 Secondary nodal characteristics

N stage	No. Of patients	Percentage
N0	2	6.67%
N1	12	40%
N2	15	50%
N3	1	3.33%

8. HISTOLOGICAL DIFFERENTIATION OF THE PRIMARY

Most of the study population 56.66% had moderately differentiated;36.67% had well differentiated cancers and 6.67% had poorly differentiated cancers.

Table 5.8 Histological differentiation of the primary

Differentiation	No. Of patients	Percentage
Well differentiated	11	36.67%
Moderately differentiated	17	56.66%
Poorly differentiated	2	6.67%

9. STAGE GROUPING

The stage grouping distribution shows most of the patients were in the locally advanced stages like stage III and stage IV A.

Table 5.9 Stage Grouping

	T1	**T2**	**T3**	**T4a**	**T4b**	**TOTAL**
N0	0	0	2(6.67%)	0	0	2(6.67%)
N1	0	0	8(26.67%)	4(13.33%)	0	12(40%)
N2a	0	0	2(6.67%)	0	0	2(6.67%)
N2b	0	0	1(3.33%)	1(3.33%)	0	2(6.66%)
N2c	0	0	6(20%)	5(16.67%)	0	11(36.67%)
N3	0	0	1(3.33%)	0	0	1(3.33%)
Total	0	0	20(66.67%)	10(33.33%)	0	30(100%)

10. STAGEWISE DISTRIBUTION

46.67% patients were grouped as stage III, 50% patients as stage IV A, and 3.33% patients in stage IV B.

Table 5.10.Stage wise Distribution

Stage	No.of patients	Percentage
STAGE III	10	33.33%
STAGE IV A	19	63.33%
STAGE IV B	1	3.33%

11. CHEMOTHERAPY CYCLES RECEIVED

Table 5.11.Chemotherapy cycles received

No. Of chemotherapy cycles received	No. Of patients	Percentage
1 CYCLE	0	0
2 CYCLES	0	0
3 CYCLES	0	0
4 CYCLES	1	3.33%
5 CYCLES	12	40%
6 CYCLES	17	56.67%

56.67% patients completed 6 cycles, 40% completed 5 cycles, and 3.33% patients received only 4 cycles of chemotherapy. The major toxicity encountered to suspend one or two cycles chemotherapy was the intense grade 3 mucositis during the last two weeks of radiation.

ACUTE LOCAL REACTIONS

Acute reactions like mucositis, skin reactions, dysphagia, xerostomia and laryngitis were scored by using **RTOG Acute Morbidity Scoring Criteria.**

13. MUCOSITIS

Table 5.13. Mucositis

MUCOSITIS	NO. OF PATIENTS	PERCENTAGE
GRADE 0	0	0
GRADE 1	0	0
GRADE 2	11	36.67%
GRADE 3	19	63.33%
GRADE 4	0	0

36.67% patients had developed patchy mucositis grade 63.33% patients had developed confluent mucositis (grade 3).

14. DYSPHAGIA

63.33% patients had developed severe dysphagia (grade 3) required nasogastric tube feeding. Remaining 36.67% patients developed moderate dysphagia (grade 2).

Table 5.14. Dysphagia

DYSPHAGIA	NO. OF PATIENTS	PERCENTAGE
GRADE 0	0	0
GRADE 1	1	3.33%
GRADE 2	10	33.33%
GRADE 3	19	63.33%
GRADE 4	0	0

15. SKIN TOXICITY

73.33% patients had patchy moist desquamation (grade 2); 26.67% patients developed dry desquamation (grade 1); 3.33% patient had confluent moist desquamation (grade 3).

Table 5.15. Skin Toxicity

SKIN REACTIONS	NO. OF PATIENTS	PERCENTAGE
GRADE 0	0	0
GRADE 1	8	26.67%
GRADE 2	21	73.33%
GRADE 3	1	3.33%
GRADE 4	0	0%

16. XEROSTOMIA

Table 5.16.Xerostomia

Toxicity of salivary gland	No. Of patients	Percentage
GRADE 0	0	0
GRADE1	21	73.33%
GRADE 2	9	26.67%
GRADE 3	0	0
GRADE 4	0	0

73.33 % of patients had dry mouth (grade 1) and thickened saliva and rest of the 26.67% of patients had moderate dryness and sticky saliva (grade 2).

17. LARYNGITIS

60% patients had mild hoarseness of voice (grade 1); 30% patients persistent hoarseness of voice (grade 2) and 10% patients developed whispered speech (grade 3).

Table 5.17.Laryngitis

Laryngitis	No. Of patients	Percentage
GRADE 0	0	0
GRADE 1	18	60%
GRADE 2	9	30%
GRADE 3	3	10%
GRADE 4	0	0

SYSTEMIC TOXICITIES

Grading of Nausea and vomiting by Common Terminology.

CRITERIA FOR ADVERSE EVENTS CTCAE VERSION 4.

18.NAUSEA:

13.33% patients had loss of desire for food without alteration in food habit (grade 1); 33.33% patients had diminished oral intake without significant weight loss and dehydration due to nausea (grade 2) and 53.33% patients were put on nasogastric tube because of inadequate oral and fluid intake (grade 3 nausea)

Table 5.18. Nausea

Nausea	No.of patients	Percentage
GRADE 1	4	13.33%
GRADE 2	10	33.33%
GRADE 3	16	53.33%

19.VOMITING

80% patients had once or twice vomiting during the day of chemotherapy (grade 1) and remaining patients had 3 to 5 episodes of vomiting in 24 hours. None had grade 3 vomiting (6 times)

TABLE 5.19 Vomiting

Vomiting	No .of patients	Percentage
GRADE 1	24	80%
GRADE 2	6	20%
GRADE 3	0	0
GARDE 4	0	0
GRADE5	0	0

HEMATOLOGICAL TOXICITY

Assessed by the RTOG Acute Morbidity Scoring Criteria.

20.ANEMIA

10 patients had hemoglobin >11 gm%(grade **0** anemia);16 patients had a fall during treatment with hemoglobin between 9.5 and 11 gm%(grade 1 anemia);4 patients developed a greater fall and their hemoglobin was between 7.5 and 9.4 gm%(grade 2).

Table 5.20.Anemia

Anemia grade	No. Of patients	Percentage
GRADE 0	10	33.33%
GRADE 1	16	53.33%
GRADE 2	4	13.33%
GRADE 3	0	0

21.LEUCOPENIA

Table 5.21 Leucopenia

Toxicity grade	No. Of patients	Percentage
GRADE 0	26	86.67%
GRADE 1	4	13.33%
GRADE 2	0	0
GRADE 3	0	0
GRADE 4	0	0

86.67% patients had Total counts ≥4000 cells/cubic millimeter (grade 0 leucopenia) and remaining 13.33% patients total counts between 3000 and <4000 cells /cubic millimeter (grade 1 leucopenia).

22. THROMBOCYTOPENIA

Table 5.22. Thrombocytopenia

Toxicity grade	No. Of patients	Percentage
GRADE 0	29	96.67%
GRADE 1	1	3.33%
GRADE 2	0	0
GRADE 3	0	O
GRADE 4	0	0

96.67% patients had a normal platelet count >100,000 cells per cubic millimeter during treatment (grade 0) and 1patient had grade 1 thrombocytopenia (75,000 to 100,000 cells per cubic millimeter).

PROGNOSTIC FACTORS DETERMINING THE TUMOR OUTCOME

AGE:

People aged more than 50 years achieved a higher complete response 80% compared to 73.32% for people less than or equal to 50 years. Partial response was lower in the age group above 51 years 20% as against 26.68% in lower age group. But this finding is not statistically significant.

GENDER

Males had more complete response than partial response. Females showed more complete and no partial response. The finding is not statistically significant.

STAGE

Stage III patients had 80% complete response. Stage IV patients had75% complete response and 25% had partial response. This finding is also not statistically significant.

CHEMOTHERAPY

Patients who received 6 cycles of chemotherapy showed 76.47% complete response . In patients who received 4- 5 cycles of chemotherapy had 76.92% complete response. This is not statistically significant.

DURATION OF RADIOTHERAPY

Overall treatment time as per protocol was 42 days.33.33% patients were able to complete treatment with ~3 days treatment interruption. Patients who had completed treatment an overall treatment time of ≤45 days had 80% complete response and 20% partial response. patients who were treated with a overall treatment time >45 days had 75% complete response. Duration of radiation did not produce a statistically significant impact on response.

HISTOLOGICAL DIFFERENTIATION OF THE PRIMARY

25 out of the 30 primaries showed a complete response (83.33%). Moderately differentiated cancer patients had better response to chemoradiation. Moderately differentiated cancers showed 88.24% complete response rates and 11.76% partial response rate; poorly differentiated cancers had 100% complete response rate and well differentiated tumors showed good response rate. This finding was statistically significant.

Table 5.23.Histologic Differentiation and Tumor Response

Differentiation	Complete response	Partail response
Well differntiated	6(54.54%)	5(45.46%)
Moderately differentiated	15(88.23%)	2 (11.77%)
Poorly differentiated	2 (100%)	0

T STAGE AND RESPONSE

T3 tumors produced 90% complete response and the poorest responses 70% were seen for T4a tumors.

Table 5.25. T stage and response

T stage	Complete response	Partial response
T3	18(90%)	2(10%)
T4a	7(70%)	3(30%)

N STAGE AND RESPONSE

Better complete responses were seen in N0 and N1 nodes. Less complete responses were seen in N2 nodal disease.

Table 5.26. N stage and response

N stage	Complete response	Partial response
N0	2(100%)	0
N1	11(91%)	1(9%)
N2a	1(50%)	1(50%)
N2b	2(100%)	0
N2c	7(63.64%)	4(36.36%)
N3	0	1(100%)

STAGE GROUPING AND RESPONSE

From the table lower stages, the tumor have higher complete response. Response rate decreased in higher stage groups.

STAGE-II (T3 N0 and T3 N1) had 100% response rate. STAGE IV A have a mixed complete response rate between 50% and 100%

Table 5.27. Stage grouping and response

Stage grouping	Complete response	Partial response
T3N0	2(100%)	0
T3N1	8(100%)	0
T3 N2a	1(50%)	1(50%)
T3 N2b	1(100%)	0
T3 N2c	4(66.66%)	2(33.33%)
T3 N3	0	1(100%)
T4a N0	0	0
T4a N1	3(75%)	1(25%)
T4a N2b	1	0
T4a N2c	3(60%)	2(40%)

TUMOR SUBSITE AND RESPONSE

Complete response rate were seen in hypo pharyngeal cancers (100%) and oropharyngeal cancers (90%); oral cavity cancers had the least complete response (54.54%)

5.28. Tumor subsite and response:

Subsite	Complete response	Partial response
Oropharynx	11(91.66%)	1(8.34%)
Oral cavity	6(54.54%)	5(45.46%)
Larynx	5(83.33%)	1(16.67%)
Hypopharynx	1(100%)	0

DISCUSSION

Long term benefits with conventional radiation therapy were not fully satisfied and have failure in local control. With advanced stages of head and neck cancer , the problems of intrinsic radio resistance, sublethal damage repair by tumor cells, hypoxia and tumor repopulation. To aim at improved therapeutic ratio hyperfractionated or accelerated fractionation has been widely tried in various clinical setting. The combination of chemoradiotherapy with modified fractionation schedules improve the results of advanced head and neck cancer.

Our study is designed at treatment of locoregionally advanced squamous cell carcinomas of head and neck ***with hyperfractionated radiotherapy and weekly docetaxel .***

RADIATION DOSE ESCALATION

So we used a total dose of 72 Gy in a try to escalate the dose. Our study shows a dose acceleration from conventional radiotherapy by 9.09%. Theoretically dose escalation of 7% to 17% is feasible without crossing the tolerance limit of late reacting tissue. This dose escalation produces better local control by 8 to

20%. Overall survival advantage of 10% to 19% compared to conventional fractionation.

COMPARISION OF TOTAL TREATMENT TIME AND RADIATION DOSE

Overall treatment time in hyperfractionation only arm is **6.3 weeks** (79.2 Gy in 1.2 Gy bd) ; hyperfractionation with chemotherapy arm (present study 72 Gy in 1.2 Gy bd) is **6 weeks**. So the difference in overall treatment time between the present study and the pure hyperfractionation is **5%.**

Similarly the difference in the total radiation dose between the pure hyperfractionation **(79.2 Gy**) and the present study (**72 Gy) is 10%.**

So we infer that the present study is compliant with the standard definition of hyperfractionation in terms of both overall treatment time and total radiation dose.

BIOLOGICAL EFFECTIVE DOSE

Ionizing radiation hits the DNA of the cell single stranded and double stranded breaks occur. Single stranded breaks increase linearly the possibility of the cell not surviving(α cell kill) and double stranded breaks increase exponentially the failure of the cell to replicate(β cell kill).Thus the α/β values of early and late effects

are obtained. So α represents the log e of the cells killed per gray radiation whereas β is the log e of the cells killed per gray squared. *The **α/β*** considered for calculation of early reacting tissues like head and neck cancers is ~10 Gy and for late reacting normal tissues is ~3 Gy.

Biological effective dose is the total dose required to produce the same log cell kill as the schedule being studied with small number of fractions considering the inter fraction interval and the cell repopulation correction factor. Biological effective dose were calculated based on the radiobiological linear quadratic cell survival model .

By using the BED formula we are able to find out the biological effectiveness of different radiotherapy schedule taking in to account the total dose, number of fractions, dose per single fraction, α/β values of tumor or normal tissue and the repopulation correction factor.

The biological effective dose (BED) for the various fractionation schedule is calculated by the formula

$$BED = D \times \frac{(1+\ d\ )}{(\alpha/\beta)}$$

When overall time factor is included, the formula is altered as follows

$$BED = D \times \left[1 + \frac{d}{(\alpha/\beta)}\right] - \frac{0.693 \times (T-Tk)}{\alpha \times Tp}$$

where D is the total dose

d is the dose per fraction

T is the overall treatment time

Tk is the time to onset repopulation of tumor from the day of start of radiation

Tp is the constant; doubling time up to the end of radiation

Model assumed $\alpha = 0.35$ Gy; Tk is21 days for tumor and 7 days for acute mucosa; Tp is 3 days for tumor and 2.5 days for mucosa.

Early effects of the current study

$$BED \text{ in } Gy_{10} = 72 \left(1+\frac{1.2}{10}\right)$$

$$BED \text{ in } Gy_{10} = 80.64 Gy_{10}$$

$\alpha/\beta = 10$ for acutely reacting tissues like mucosa and tumor

late effects of the current study is

$$BED \text{ in } Gy_{3} = 72 \left(1+\frac{1.2}{3}\right)$$

$$BED \text{ in } Gy_{3} = 100.8 Gy_{3}$$

$\alpha/\beta = 3$ for late complications

EQD is called as the *equivalent* dose in 2 Gy [37]. It is defined as the total dose in 2 Gy that gives the equal log cell kill as the schedule studied.

For an early-responding tissue, a BED in Gy10 must be divided by 1+2/10 = **1.2** to find its EQD $_{10/2}$, using this ‘‘early’’ α/β ratio of 10 Gy.

For a late-reacting tissue BED in Gy_3 is divided by 1+2/3 =**1.67** to find its equivalent dose in 2 Gy fraction $EDQ_{3/2}$, using the same ‘‘late’’ α/β ratio, 3 Gy.

CALCULATION WITH REPOPULATION CORRECTION

Tk is21 days for tumor cells and 7 days for mucosa; **Tp** is 3 days for tumor and 2.5 days for mucosa.

$$\text{BED in Gy}_{10} \text{ for mucosa} = 72 \times \left[1 + \frac{1.2}{(3)}\right] - \frac{0.693 \times (40-7)}{}$$

$$= 0.35 \times 2.5$$

$$= 80.64 - 26.13$$

$$= 54.51\ Gy_{10}$$

$$\text{EQD}_{10/2} = \text{BED IN GY}_{10} / 1.2$$

$$= 54.51/1.2$$

$$= 45.42\ Gy_{10/2}$$

Also using BED formula we can calculate the log cell kill for the schedule studied by using the below formula

Log 10 cell kill =BED Gy_{10} × 0.152

So first we calculate BED in gy 10 for tumor,

$$\text{BED in } Gy_{10} \text{ for tumor} = 72 \times \left[1 + \frac{1.2}{(3)}\right] - \frac{0.693 \times (40-21)}{}$$

$$= 0.35 \times 3$$

$$= 80.64 - 12.54$$

$$= 68.1\ Gy_{10}$$

Log cell kill = 68.1 × 0.152

= 10.35

11 log $_{10}$ -Log cell kill is the reduction of 10^{9} cells in a gram of tissue to a chance of one cell in 100 tumors surviving the radiation. The best head and neck radiotherapy schedule delivers **11 to 11.2 log $_{10}$ cell kill [37].**

CLINICAL INTERPRETATION OF THE RADIOBIOLOGICAL PARAMETERS

By restraining the late BEDs equivalent to 70 Gy in 2 Gy fractions we avoid the major late complications in head and neck irradiation. The major limiting factor in dose escalation in any form of altered fractionation schedule are the acute tissue reactions like

mucositis and dysphagia. When a new radiotherapy schedule is to be tested the calculation using BED early and late effects; By using EQD $_{3/2}$ Gy formulae able to know whether the schedule is toxic or not.

From the calculations it is evident that the present study fractionation schedule shows

- The least late reacting normal tissue toxicity(100.8Gy_3)
- Biological effective dose for early reacting normal tissue (80.86 Gy_{10}) like mucosa is comparable to those produced by conventional RT (79.2 Gy_{10})**.**
- **Acute mucosal EQD** is **45.42 Gy $_{10/2}$ which is well within the grey zone.**
- **Log cell kill of hyperfractionated radiotherapy is 10.35 and is higher than the conventional schedule.**

It is explained that our study using hyperfractionation produces a log cell kill greater than conventional radiation; a mucosal EQD_2 well within the grey zone and a least late tissue reactions.

BIOLOGIC EFFECTIVE DOSE OF ACUTE AND LATE REACTING TISUES IN VARIOUS TREATMENT SCHEDULES

Radiotherapy Fractionation Schedules	total dose Gy	overall treatment time (days)	acute BED Gy10	late BED Gy3	acute mucosal EQDGy 10/2	log cell kill
Conventional RT 33×2 Gy	66	45	79.2	110	44.22	10.13
Strong Conventional 35× 2 Gy	70	47	84	116.7	44.26	10.26
Accelerated concomitant boost 30×1.8 Gy + 12×1.5 Gy	72	39	84.4	113.4	49.21	11.02
Pure Hyperfractionated RT 68 × 1.2 Gy	81.6	45	91.39	114.2	51.08	11.48
Continuous Hyperfractionated Accelerated Radiotherapy 36 × 1.5 Gy Tds/12 Days	54	12	62.1	81	48.45	10.34
Our Study Chemo Hyperfractionation 60 × 1.2	72	40	80.86	100.8	45.42	10.35

Acutely reacting normal tissues have rapid cell turnover and highly sensitive to radiation. Radiosensitivity of tumor tissue is like to those of acutely reacting normal tissues. Hyperfractionation is advantageous in the tumors with low fractionation sensitivity by

α/β values that are greater than those for late reacting normal tissues.

OUTCOMEANALYSIS

Our study showed a acceptable toxicity and high response rate similar to other hyperfractionation studies by Pinto et al, 1991;Horiot et al, 1992; Cummings et al, 1996; Fu et al, 2000 and Jeremic et al, 2000.The overall response rates assessed at the end of 6 weeks of hyperfractionated radiochemotherapy in our study is 100% .Complete response rate of 62% achieved in our study.

Also the most essential finding from our study is that hyperfractionated radiochemotherapy is enormously beneficial to the subset of patients with advanced primary and nodal disease as in opposition to the conventional fractionation; which is also more beneficial in treating the earlier stage disease.

TO SUM UP

- **Female sex** showed higher complete responses than male.
- **Stage-III** Cancers Shows Higher Complete Responses Than Stage Iv A
- **Moderately and poorly differentiated cancers showed a considerable** complete response.

- **Lower the t stage** higher is the complete response
- **Lower the n stage** higher is the complete response
- **Lower the tnm stage group** higher is the complete response.
- **Hypopharyngeal and oropharyngeal tumors** produced greater complete response.
- Complete response rate in primary T3 and T4a tumors are 90% and 70% respectively.
- Complete response rates attained by N0, N1, N2a, and N2c nodes are 100%, 90%, 50% and 63% respectively.
- **Primary and secondary complete response was achieved by 76%**
- High complete responses were achieved by T3N0 (1000%), T3 N1 (100%), then by T3N2a(50%),T3 N2c (66.66%),T4a N1 (70%) and last by T4a N2c (60%)

SIDE EFFECTS

- 63.33% had grade 3 mucositis.
- 73.33% had grade 2 and 3.33% had grade 3 skin toxicities
- 10% had grade 3 laryngitis.

- No Grade 3, 4 hematological toxicities in anemia
- No Grade 3, 4 hematological toxicities in leucopenia or thrombocytopenia were observed.
- There was no grade III or IV vomiting.

LIMITATIONS

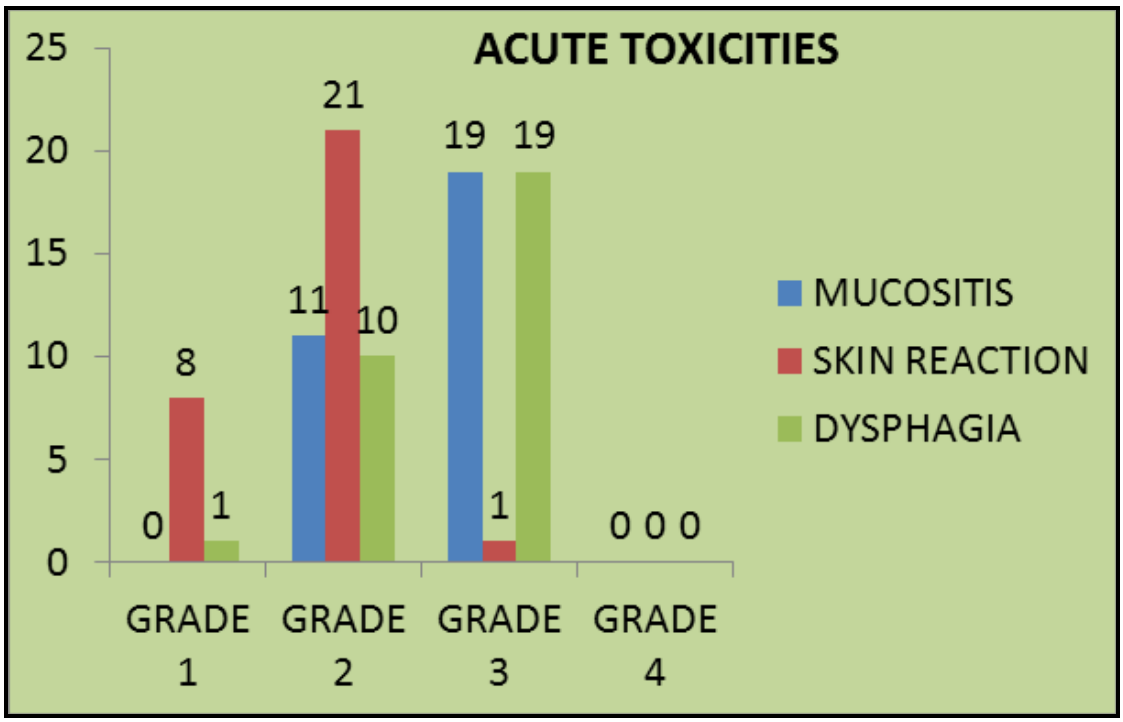
Limitations of the study were the treatment delivery with cobalt 60- machine; the small number of study population. There is no powerful consensus for altered fractionation like hyperfractionation with chemotherapy.

This protocol needs to be tested in a larger patient population in a phase III randomized control trial.

CONCLUSION

Our study shows complete response rate (**76.66%**) this results are comparable with other international studies as mention in the literature. **30** patients completed the planned chemoradiotherapy with minimal treatment interruptions. Acute toxicities were acceptable and manageable. Differentiation of the primary lesions considerably influences the outcome.

From our study, treatment protocol of loco regionally advanced unresectable squamous cell carcinomas of head and neck with concurrent weekly docetaxel 20 mg / m^2 is tolerable and feasible in our population.


ACUTE TOXICITIES
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15
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5
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0
8
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19
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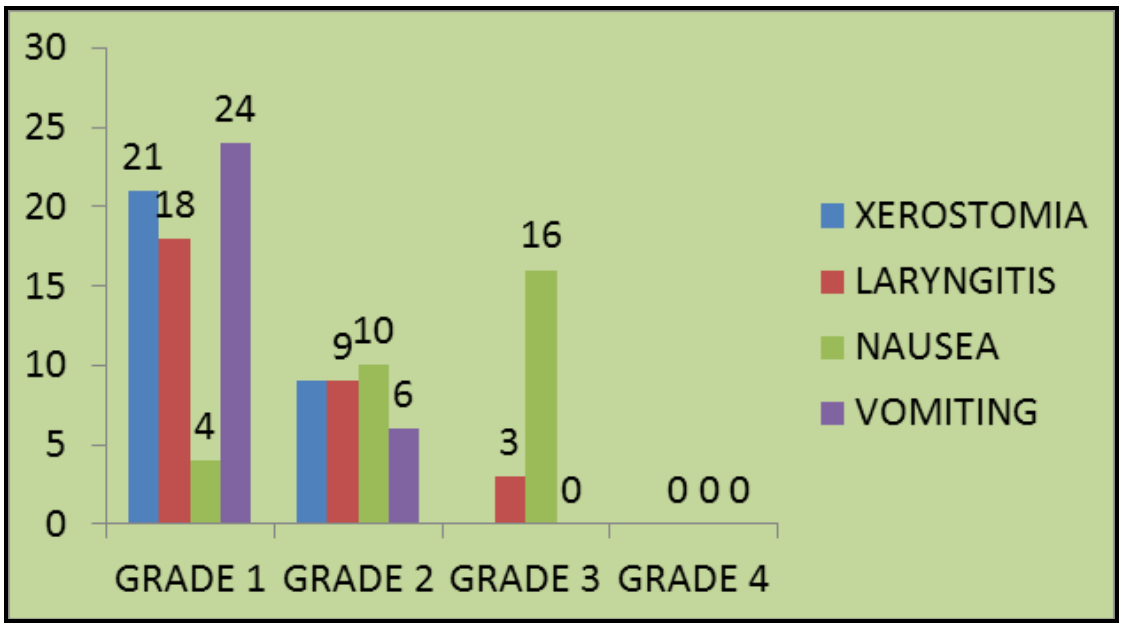
GRADE 2
GRADE 3
GRADE 4
MUCOSITIS
SKIN REACTION
DYSPHAGIA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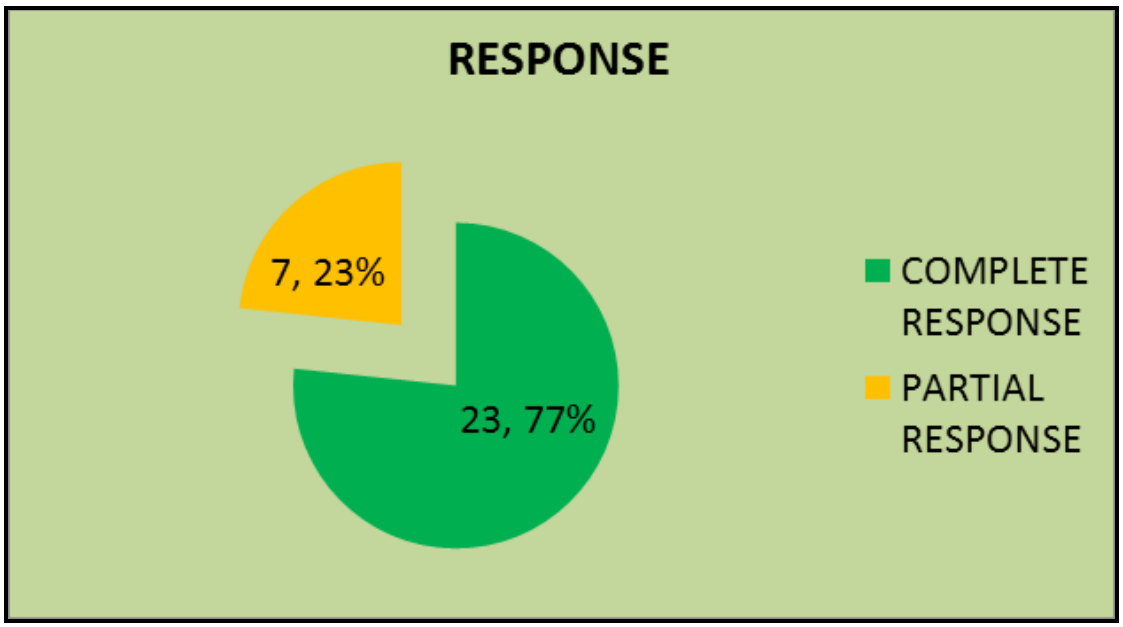
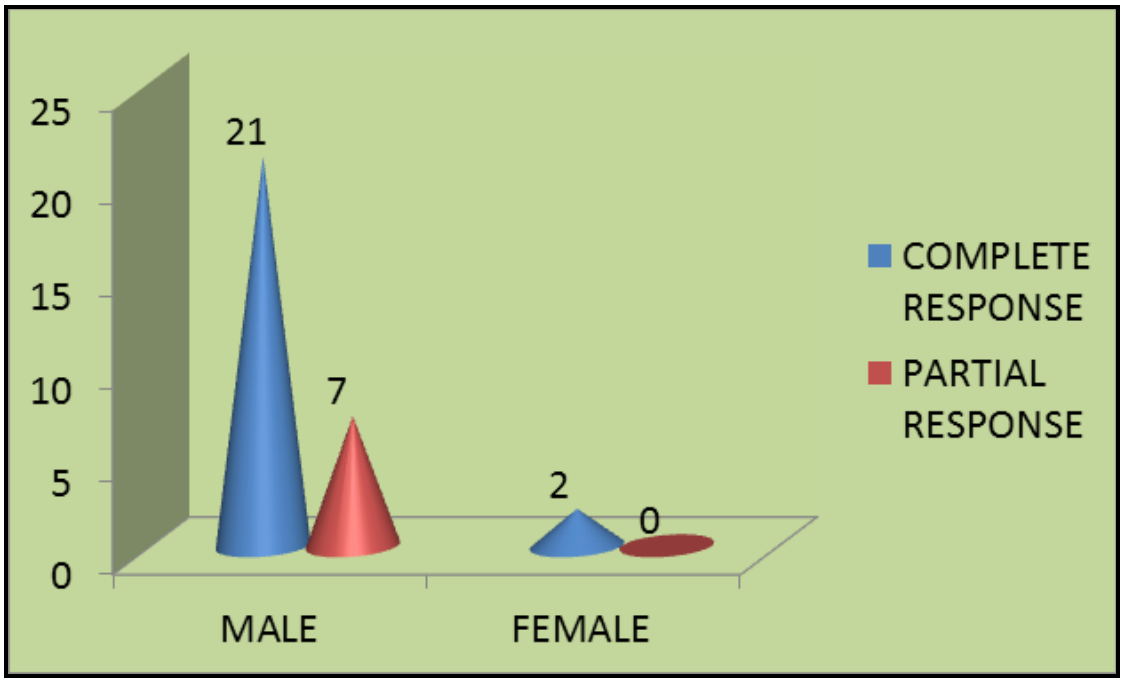
GRADE 4
XEROSTOMIA
LARYNGITIS
NAUSEA
VOMITING


RESPONSE
7, 23%
23, 77%
COMPLETE RESPONSE
PARTIAL RESPONSE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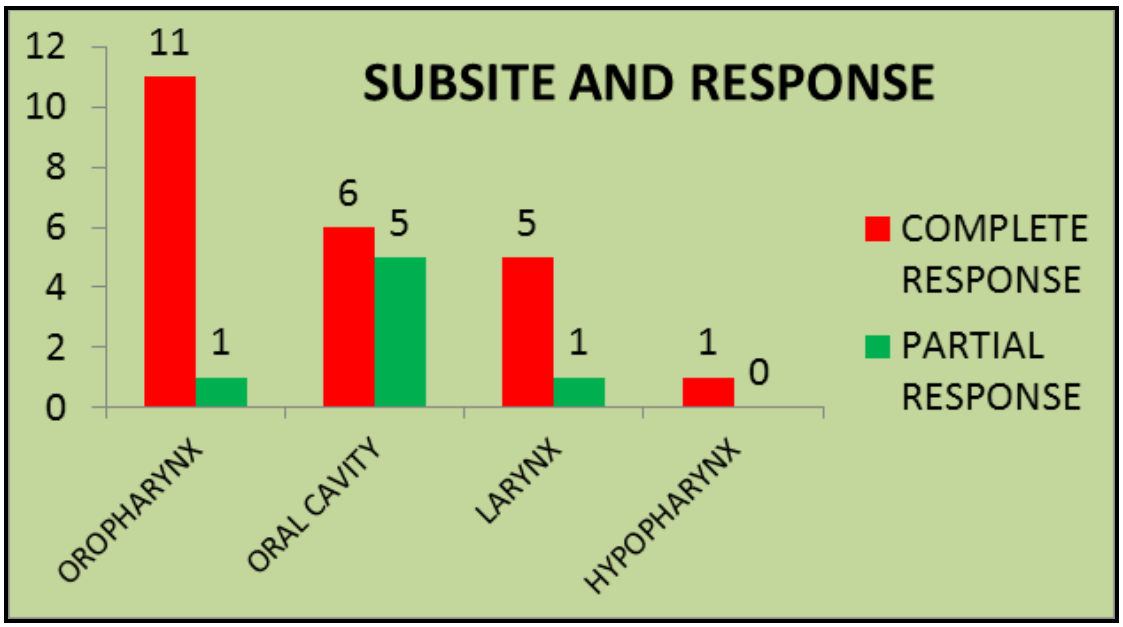
MALE
FEMALE
COMPLETE RESPONSE
PARTIAL RESPONSE


SUBSITE AND RESPONSE
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10
8
6
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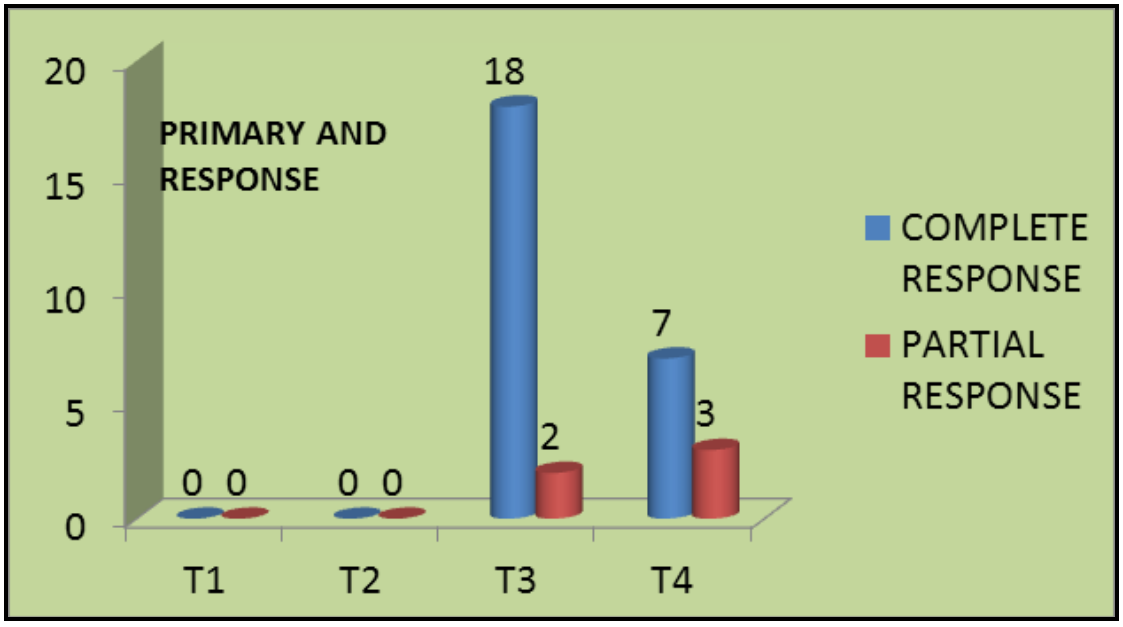
2
0
11
1
6
5
5
1
1
0
OROPHARYNX
ORAL CAVITY
LARYNX
HYPOPHARYNX
COMPLETE RESPONSE
PARTIAL RESPONSE


PRIMARY AND RESPONSE
20
15
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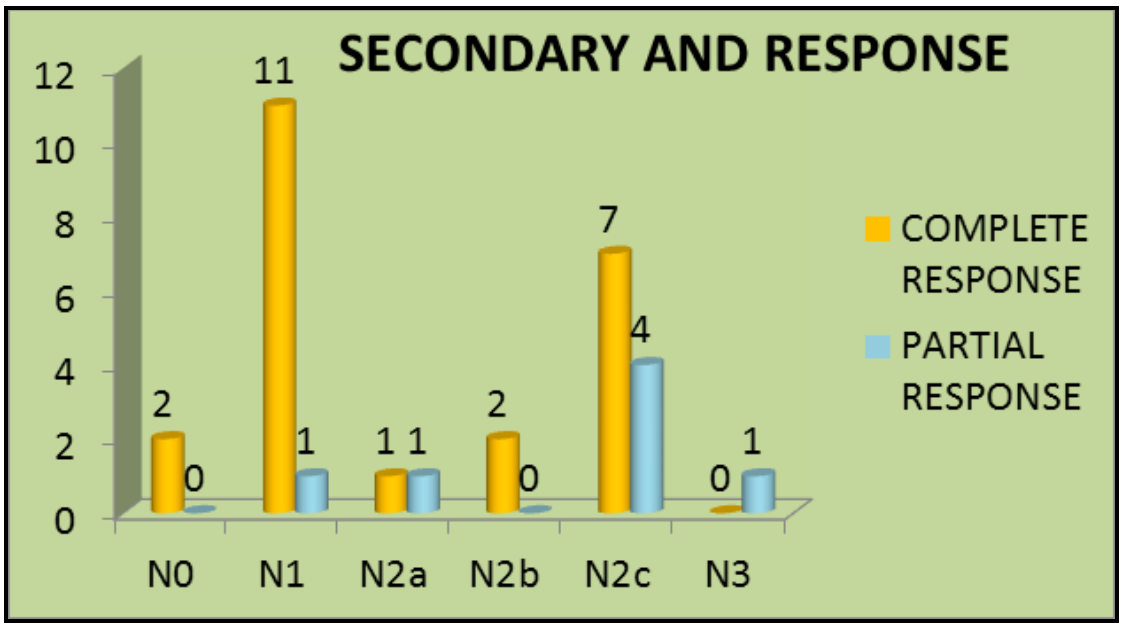
T1
T2
T3
T4
COMPLETE RESPONSE
PARTIAL RESPONSE


SECONDARY AND RESPONSE
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11
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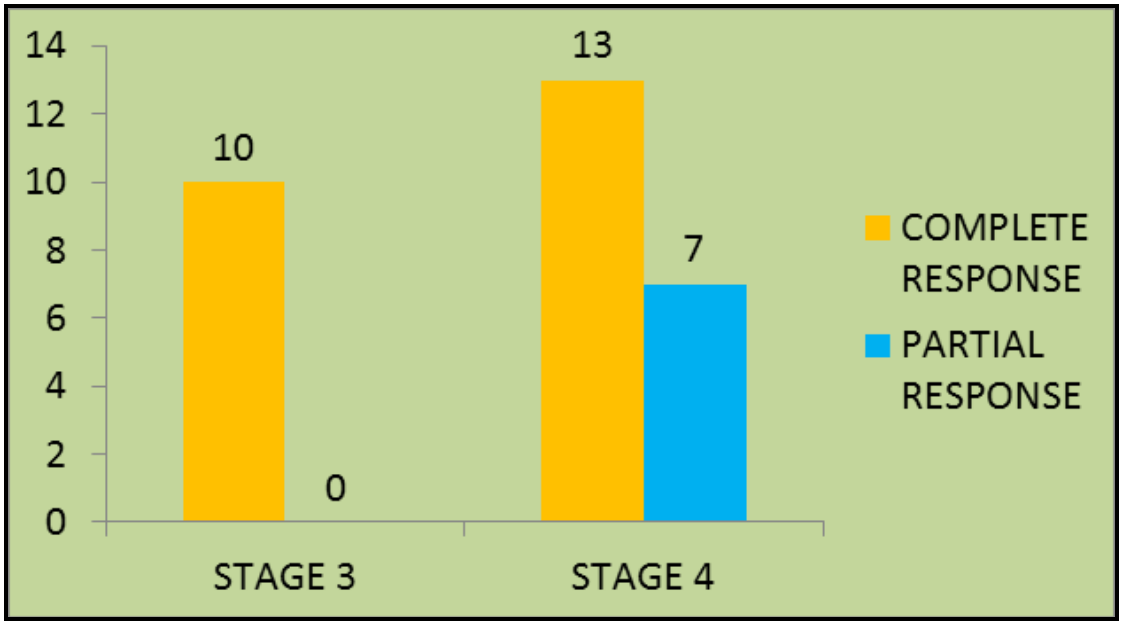
1
N0
N1
N2a
N2b
N2c
N3
COMPLETE RESPONSE
PARTIAL RESPONSE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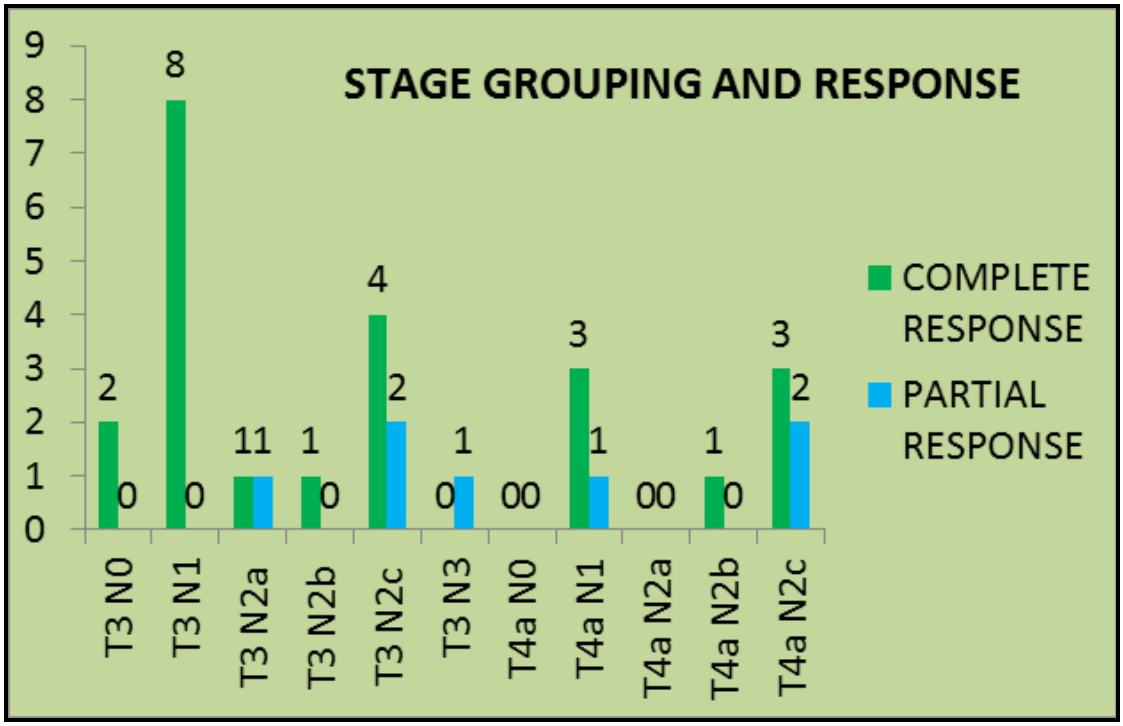
13
7
STAGE 3
STAGE 4
COMPLETE RESPONSE
PARTIAL RESPONSE


STAGE GROUPING AND RESPONSE
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7
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5
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1
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0
8
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3
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1
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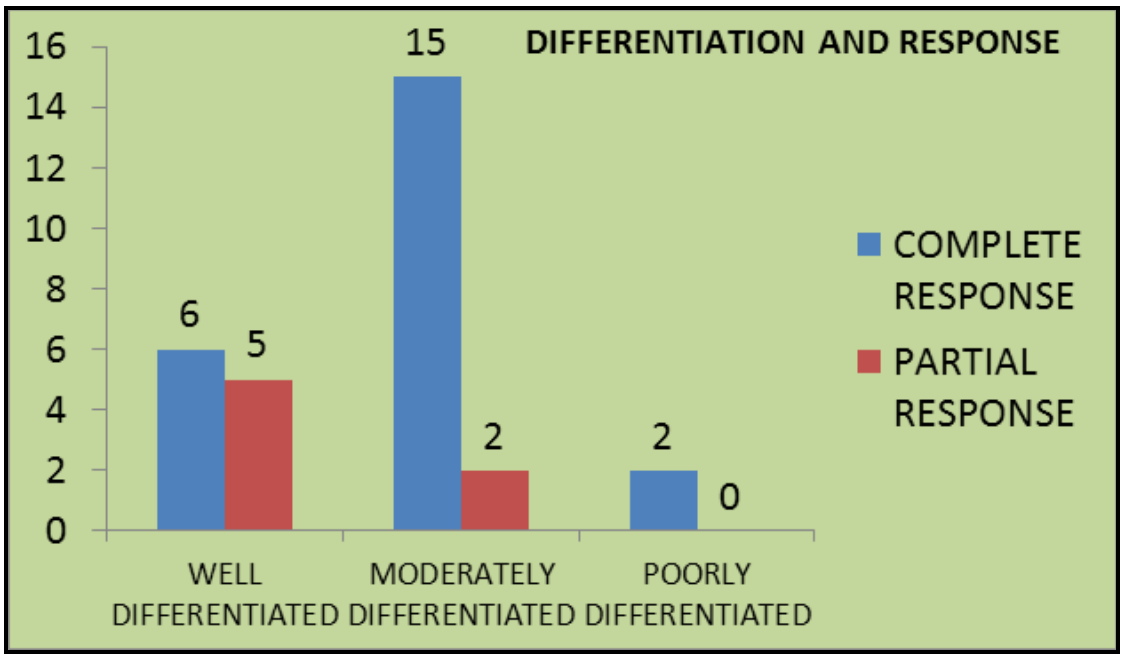
3
2
T3 N0
T3 N1
T3 N2a
T3 N2b
T3 N2c
T3 N3
T4a N0
T4a N1
T4a N2a
T4a N2b
T4a N2c
COMPLETE RESPONSE
PARTIAL RESPONSE


DIFFERENTIATION AND RESPONSE
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14
12
10
8
6
4
2
0
6
5
15
2
2
0
WELL DIFFERENTIATED
MODERATELY DIFFERENTIATED
POORLY DIFFERENTIATED
COMPLETE RESPONSE
PARTIAL RESPONSE

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ANNEXURE I

RTOG - ACUTE RADIATION MORBIDITY SCORING CRITERIA

Grade	0	1	2	3	4
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
mucous membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
pharynx & esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis

		metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals			
laryngitis	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

HEMATOLOGICAL TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-

GUIDELINES: The criteria are relevant from day 1, the commencement of therapy, through day 90. All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator. Any toxicity which caused death is graded 5.

ANNEXURE II

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS CTCAE VERSION 4.

GRADE	1	2	3	4	5
NAUSEA	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition.	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated.	-	-

Grade	1	2	3	4	5
vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tube feeding,TPN or hospitalization indicated	Life-threatening consequences,urgent intervention indicated	death

INFORMATION TO PARTICIPANTS

TITLE: ROLE OF HYPERFRACTIONATED RADIOTHERAPY WITH WEEKLY DOCETAXEL IN LOCALLY ADVANCED UNRESECTABLE HEAD AND NECK CANCER

Principal investigator: Dr.JEYASANKAR.S

Name of the participant:

Site: Department of Radiotherapy, Madras Medical College & RGGGH, Chennai-3.

You are invited to take part in the research/study/procedure. The information in this document is meant to help you decide whether or not to take part.Please feel free to ask if any queries.

What is the purpose of the study?The incidence of head and neck cancer has been increasing worldwide .Local recurrences is a major problem after intensive curative treatment. With our treatment methodology we are aiming to give a better quality of life for the patient by achieving a better immediate locoregional response and less treatment related toxicity.

We have obtained permission from the Institutional Ethics Committee.

The study design: Single arm prospective study.

Study procedures: Patients will need to undergo blood investigations, CT scan neck, Xray chest, dental prophylaxis and smoking cessation counselling, if smoker which were done routinely in all head and neck cancer patients. These tests are essential to assess the status of the disease. The purpose of this study is to find the use of weekly Docetaxel concurrently with radiotherapy is feasible in LAHNC and whether it will have a better response rate.

Possible risks to you: None greater than patients receiving standard radiotherapy.

Possible benefits to you: Better response at the tumour less toxicity from treatment.

Possible benefits to other people: The results of the research mat provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from you: You have the right to confidentiality regarding the privacy of your medical information[personal details, physical examination, investigations and your medical history]. B y signing this document you will be allowing the research team investigators, other study personal, Institutional ethics committee and any person or agency required by law like the drug controller general of India to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution.You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at time during the course of the study without giving any reasons. You will still continue to receive the standard treatment if you decide so. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of investigator **Signature of the participant**

INFORMED CONSENT FORM

TITLE: ROLE OF HYPERFRACTIONATED RADIOTHERAPY WITH WEEKLY DOCETAXEL IN LOCALLY ADVANCED UNRESECTABLE HEAD AND NECK CANCER

NAME OF THE PARTICIPANT:
NAME OF THE PRINCIPAL INVESTIGATOR: DR.S.JEYASANKAR,
NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

I_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer
unusual symptoms. *****
8. I have not participated in any research study within the past 12month(s). *****
9. I agree to undergo complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors,

regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு

தலை மற்றும் கழுத்துப் பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு நோய்குறி தணிப்பு கதிர்வீச்ச கீமோதெரபியுடன் கதிர்வீச்சின் பயனை அதிகரிக்கக் கூடிய டோசிடேக்சல் என்னும் மருந்து செலுத்துதல்.

ஆய்வாளர் :

பங்கேற்பாளர்:

இந்த ஆய்வு ராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம்:

மாறிவரும் பொருளாதார காரணிகள் மற்றும் வாழ்க்கைமுறையின் காரணமாக தலை மற்றும் கழுத்துப்பகுதி புற்றுநோயினால் பாதிக்கப்பட்டவர்களின் எண்ணிக்கை சமீபகாலமாக அதிகரித்துக்கொண்டே வருகிறது.

பெரும்பாலானோர் இந்த நோய் முற்றிய நிலையிலேயே மருத்துவமனைக்கு வருகின்றனர். அதனால் முழுவதும் குணப்படுத்தக்கூடிய வைத்திய முறைகளை பயன்படுத்தும் வாய்ப்பை இழக்கின்றனர். அதனால் நோய்க்குறி தணிப்பு வைத்திய முறைகளை மட்டுமே பயன்படுத்தும் நிலைக்கு ஆளாகின்றனர். இவ்வகையான வைத்தியத்தில் பலவகை உள்ளன. இந்த ஆய்வில் பயன்படுத்தும் வைத்திய முறையின் மூலம் சிறந்த நோய்க்குறி தணிப்பையும் குறைவான பின்விளைவுகளையும் பெரும் வகையில் வழி செய்வதே எங்கள் நோக்கமாகும்.

ஆய்வின் செயல்முறை:

நோயாளிகள் இரத்தப் பரிசோதனை, முகம் மற்றும் கழுத்துப்பகுதி சிடிஸ்கேன், நெஞ்சுப்பகுதி எக்ஸ்-ரே, பல் சுத்தம் மற்றும் பாதுகாப்பு, புகைப்பழக்கத்தை கைவிட ஆலோசனை முதலியவற்றை மேற்கொள்ள வேண்டும். இவை அனைத்தும் வழக்கமாக எல்லா புற்றுநோயாளிகளிடமும் நோயின் நிலையை அறிய மேற்கொள்பவையே. நோயாளிகளுக்கு தினமும் இருமுறை 5 நாட்கள் 6 வாரங்களுக்கு நோய்குறி தணிப்பு கதிர்வீச்சுடன் வாரம் ஒருமுறை டோசிடேக்சல் எனும் மருந்து செலுத்தப்படும்.

ஆறு வாரங்கள் கழித்து நோயின் நிலையை அறிய சிடிஸ்கேன் மற்றும் உடல் பரிசோதனை செய்யப்படும். இந்த பரிசோதனைகள் இவ்வகையான வைத்தியத்தின் விளைவுகள் மற்றும் பயன்களை அறிய அவசியம்.

ஆய்வினால் ஏற்படும் நன்மைகள்

சிறந்த நோய்க்குறி தணிப்பும், குறைவான பின்விளைவுகளும் கிடைக்க அதிக வாய்ப்புகள் உள்ளன.

ஆய்வினால் ஏற்படும் தீமைகள்

வழக்கமான சுதிர்வீச்சுகளில் வரும் விளைவுகளைவிட அதிகம் ஏதுமில்லை.

ஆய்வினால் பிறருக்கு ஏற்படும் நன்மைகள்:

இந்த ஆய்வில் கலந்துகொள்வதன் மூலமாக நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் ரகசியமாக பாதுகாக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

கதிர்வீச்சு சிகிச்சை அளிக்கபடும் இடத்திலுள்ள தோல் பராமரிப்பு

செய்	செய்யாதே
• சிகிச்சை அளிக்கப்படும் முந்தைய நாள் மட்டும் முகச்சவரம் செய்யலாம்.	• சிகிச்சையின் போதோ ,சிகிச்சை இடைவெளியின் போதோ (சனி,ஞாயிறு) முகச்சவரம் செய்யக்கூடாது.
• தோல் உரின்தலோ சிவந்தாலோ மருத்துவரை அணுக வேண்டும்.	• சிகிச்சை கிடைக்கும் இடத்தில் தண்ணீரோ வியர்வையோ படக்கூடாது. • அதன் மேல் தேங்காய் எண்ணெய்,வாசலின் ,முகபவுடர், மஞ்சள் தடவகூடது . • துணி வைத்து தோலை தேக்கக்கூடாது.
வாய் பராமரிப்பு • மருத்துவர் கூறிய அளவில் சமையல் உப்பு மற்றும் ஆப்ப சோடா உப்பு ஆகியவற்றை தண்ணீரில் கலந்து நாலு -ஆறு முறை வாயை கொபளிக்க வேண்டும் . • குழந்தைகள் பிரஷ் கொண்டு பல் துலக்கலாம் . • மருத்துவர் கூறிய மருந்தை மட்டும் உபயோகிக்கவும் .	• அதிக அளவு வெயிலோ குளிரோ அதன் மேல் படக்கூடாது.

செய்	செய்யாதே
• அதிக காரம் எண்ணெய் சேர்க்ககூடாது (ஊறுகாய்) • டீ காபி தவிர்க்கவும்.	• புகை பிடிக்கக்கூடாது, மது அருந்தக்கூடாது .
• ஆப்பில் வாழை பழம் சிறிய துண்டுகளாகவோ பழச்சரகவோ குடிக்கலாம். • தினம் ஒரு வேகவைத்த முட்டை சாப்பிடலாம். • வேக வாய்த்த காய்கறிகளை மட்டும் சாப்பிடுங்கள் .	• சிப்ஸ் மிச்சர் காரசேவ் போன்றவற்றை தவிர்க்கவும்.
• பழங்களில் திராட்சை ,எலுமிச்சை தக்காளி தவிர்க்கவும். • தினம் இரண்டு கப் பால் (பூஸ்ட் ஹார்லிக்ஸ்)குடிக்கவும். • வேக வைத்த துவரம் பருப்பு,பாசி பயறு ,சுண்டல், உருளை கிழங்கு சாப்பிடலாம் . • பாலில் தோய்த்த ரொட்டிதுண்டுகள் சாப்பிடலாம் . • எளிதில் ஜீரணம் ஆகக்கூடிய உணவை மட்டும் சாப்பிடுங்கள் . • காய்கறி சூப் ,மட்டன்,சிக்கன் சூப் குடிக்கலாம் .	• வெற்றிலை பாக்கு மூக்குப்பொடி பான்பராக், ஹான்ஸ் ,மாவா கண்டிப்பாக பயன் படுத்தக்கூடாது .

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Jeyasankar S
Post Graduate in Radiotherapy
Madras Medical College
Chennai 600 003

Dear Dr. Jeyasankar S

The Institutional Ethics Committee has considered your request and approved your study titled **"ROLE OF HYPERFRACTIONATED RADIOTHERAPY WITH WEEKLY INJ. DOCETAXEL IN LOCALLY ADVANCED UNRESECTABLE HEAD AND NECK CANCER"** NO.04032015.

The following members of Ethics Committee were present in the meeting hold on 03.03.2015 conducted at Madras Medical College, Chennai 3

1. Prof.C.Rajendran, MD	:Chairperson
2. Prof.R.Vimala,MD.,Dean,MMC,Ch-3	. Deputy Chairperson
3. Prof.B.Kalaiselvi,MD.,Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.R.Nandini,MD.,Inst.of Pharmacology,MMC	: Member
5. Prof.K.Ramadevi, Director ,Inst.of Bio-Chem.MMC	: Member
6. Prof.Saraswathy,MD.,Director,Pathology, MMC	: Member
7. Prof.S.G.Sivachidambaram,MD.,Director I/c Inst.of Internal Medicine,MMC	: Member
8. Thiru S.Rameshkumar, B.Com., MBA.	: Lay Person
9. Thiru S.Govindasamy, BA., BL.,	: Lawyer
10.Tmt.Arnold Saulina, MA., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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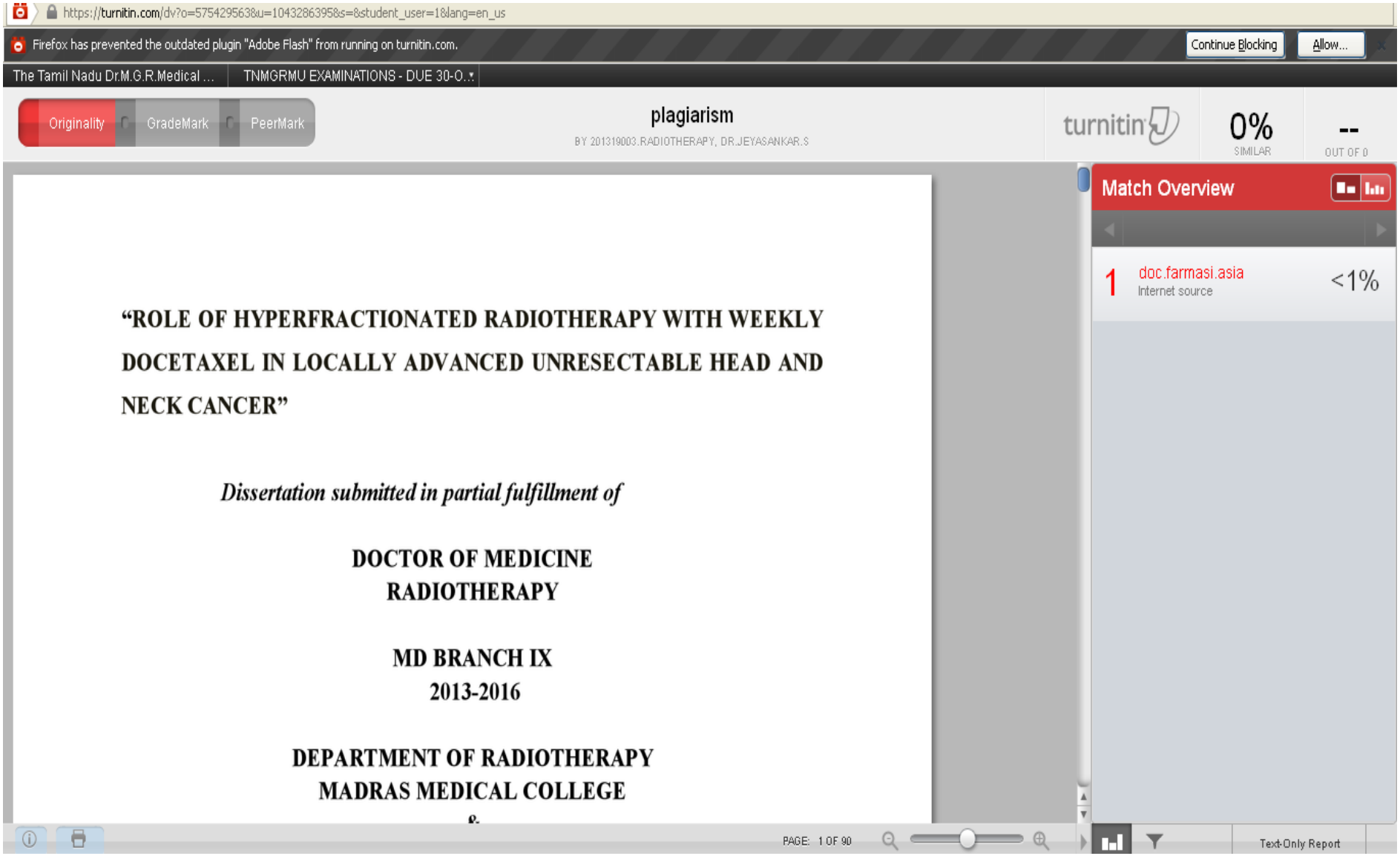
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Dissertation submitted in partial fulfillment of
DOCTOR OF MEDICINE
RADIOTHERAPY
MD BRANCH IX
2013-2016
DEPARTMENT OF RADIOTHERAPY
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